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Prognostic Value of a Novel Lactate-shock Index for 28-day Mortality in Adult Sepsis Patients

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Abstract

Aim: Early and accurate diagnosis of sepsis allows for the timely initiation of appropriate treatment, which can improve clinical outcomes. Studies have shown that the shock index (SI) and high lactate levels are successful in predicting mortality and adverse outcomes in various clinical situations. However, the variability in lactate levels due to various factors limits its usability when used alone. Considering these limitations, we aimed to evaluate the performance of a combined lactate SI (LSI) in predicting 28-day mortality in patients with sepsis.

Methods: Patients aged 18 and over who were diagnosed with sepsis between 15.02.2023 and 15.12.2023 and presented to the emergency department (ED) were included in the study. Sepsis diagnosis was evaluated according to the criteria in the sepsis-3 guidelines. Data collection for patients presenting to the ED with suspected sepsis included demographic findings such as age and gender. Glasgow coma scale score; vital signs including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), body temperature (°C), and respiratory rate (breaths/min). The SI, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-monocyte ratio, and LSI values were calculated and recorded in the data collection form.

Results: The study included a total of 77 patients, with 28-day mortality occurring in 31 patients (40.3%). Multivariate logistic regression analysis identified SI [Odds ratio (OR), 9.623, p=0.023] and LSI (OR: 1.333, p=0.029) as independent prognostic indicators of 28-day mortality. In the receiver operating characteristic analysis, LSI [area under the curve (AUC): 0.710] outperformed both SI (AUC: 0.690) and lactate (AUC: 0.681).

Conclusion: This study demonstrates that LSI is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index showed better performance than both lactate and SI in predicting 28-day mortality.

Keywords: Emergency medicine, lactate, mortality, sepsis, shock index

Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction due to an inappropriate host response secondary to infection (1). It is among the common causes of infection-related deaths and is associated with high morbidity and mortality. Sepsis affects approximately 30 million people globally each year, resulting in death in about 6 million of these patients (2,3). Despite current advancements in diagnosis and treatment, mortality rates remain high in sepsis, particularly in septic shock (1,4).

Early and accurate diagnosis of sepsis allows for the timely initiation of appropriate treatment, which can improve clinical outcomes (3,5). Emergency departments (EDs) are often the first point of contact for patients suspected of sepsis. However, due to the nature of EDs, there is limited time for evaluating and initiating treatment for these patients. Early identification of high-risk patients in ED is important due to the benefits of early initiation of appropriate treatment, identification of patients with critical care needs, and improvement in patient survival outcomes (1,5). Due to limited resources and time

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constraints in ED, practical and rapid risk stratification tools are needed (6).

The shock index (SI), defined as the ratio of heart rate (HR) to systolic blood pressure (SBP), is an easily calculable index at the bedside (6). The literature has demonstrated the success of SI in predicting mortality and adverse outcomes in various clinical situations such as sepsis, trauma, and pulmonary embolism (4,7-10). Lactate, a product of anaerobic metabolism, is an indicator of hypoperfusion and tissue hypoxia. Studies in critically ill patient groups have shown that elevated lactate levels are associated with mortality (11,12). Serum lactate levels above 2 mmol/L have been proposed as a new criterion for defining septic shock in the sepsis-3 guidelines. While studies have shown that high lactate levels are strong predictors of disease severity and mortality, low lactate levels are associated with improved clinical outcomes (11,13,14). However, lactate levels can also rise due to metformin use, liver and kidney failure, and malignancies, limiting their usability when used alone (15). Considering the limitations of lactate levels, we developed a combined lactate SI (LSI) obtained by multiplying lactate by SI and aimed to evaluate the performance of this new index in predicting 28-day mortality in patients with sepsis.

Materials and Methods

Compliance with Ethical Standards

This study was conducted prospectively in the ED of a tertiary hospital following approval from the Ordu University Clinical Research Ethics Committee (approval no.: 2023/41, date: 03.02.2023). The study was conducted in accordance with the ethical rules and principles of the Helsinki Declaration at all stages. Written and verbal consent was obtained from the participants.

Study Design and Selection of Participants

Patients aged 18 and over who were diagnosed with sepsis between 15.02.2023 and 15.12.2023, presented to the ED, and who read and accepted the consent form were included in the study. Sepsis diagnosis was evaluated according to the criteria in the sepsis-3 guidelines.

Exclusion criteria included pregnant women, patients under 18 years of age, patients presenting to the ED with cardiac arrest, those with chronic liver failure, chronic kidney failure, a history of chronic heart failure affecting SBP, bedridden immobile patients, patients diagnosed with epilepsy and presenting post-epileptic seizure, trauma patients, those who withdrew consent, and those with incomplete data in their records.

Data Collection and Measurements

Data collection for patients presenting to the ED with suspected sepsis included demographic findings such as age and gender. Glasgow coma scale score; vital signs including SBP (mmHg), diastolic blood pressure (DBP, mmHg), HR (bpm), body temperature (°C), and respiratory rate (breaths/min).

Blood samples taken according to sepsis guidelines were analyzed for white blood cells, hemoglobin (mg/dL), platelets, neutrophil count, lymphocyte count, monocyte count, alanine aminotransferase (IU/L), aspartate aminotransferase (IU/L), C-reactive protein (CRP), and blood gas samples including pH, partial pressure of carbon dioxide ($PaCO_2$, mmHg), bicarbonate (mEq/L), and lactate (mmol/L).

The SI, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and LSI values were calculated and recorded in the data collection form. The calculations for these parameters are as follows:

SI=HR (bpm)/SBP (mmHg)
NLR=Neutrophil count/Lymphocyte count
PLR=Platelet count/Lymphocyte count
LMR=Lymphocyte count/Monocyte count
LSI=Lactate (mmol/L) x SI

In the ED, blood samples are collected in standardized tubes containing dipotassium ethylenediaminetetraacetic acid for complete blood counts. Plasma CRP levels are measured using a turbidimetric immunological test. Lactate levels are determined from blood gas samples collected in heparinized tubes.

The primary outcome was 28-day mortality, defined as death within 28 days from the time of ED presentation. Patients were classified as alive or deceased based on the 28-day mortality data.

Statistical Analysis

Statistical analysis was performed using SPSS v.26 and Jamovi v2.5.3. The normality of the data was assessed using visual and analytical methods. Descriptive statistics were presented as mean ± standard deviation, median (25^{th} and 75^{th} percentiles), and frequency (n and %). Based on the continuous and categorical characteristics of the variables, as well as the results of the normality analysis, appropriate analyses were performed using the independent samples t-test, Mann-Whitney U test, and chi-square test.

Multivariate logistic regression analysis was conducted to evaluate whether lactate, SI, and LSI were independent predictors of 28-day mortality. The odds ratios (ORs) of the variables were calculated with a 95% confidence interval (CI). Receiver operating characteristics (ROC) analysis was applied to evaluate the diagnostic performance of the variables. Cut-off points were calculated using the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated based on

the cut-off points for predicting 28-day mortality. A p-value of <0.05 was considered statistically significant.

Results

The study included a total of 77 patients, aged 43-94 years, who met the inclusion and exclusion criteria. The mean age of the patients was 72.01±10.86 years, and the majority were male (63.6%). Twenty-eight-day mortality was observed in 31 patients (40.3%). Table 1 shows the relationship between the patients' demographic, clinical, and laboratory findings and 28-day mortality. No statistical difference was found between the deceased and surviving patient groups in terms of gender and age (p=0.272 and p=0.174). Deceased patients had lower SBP (p=0.020) and higher HR (p=0.049). Lactate, SI, and LSI were higher in deceased patients (p-values of 0.005, 0.005, and 0.001, respectively).

Univariate logistic regression analysis revealed that lactate (OR: 1.707, 95% CI 1.195-2.438, p=0.003), SI (OR: 6.447, 95% CI 1.568-26.51, p=0.010), and LSI (OR: 1.448, 95% CI 1.157-1.814, p=0.001) were positively and statistically significantly associated with 28-day mortality. Multivariate logistic regression analysis was performed to assess the independent effects of these variables on

Table 1. Relationship with 28-day mortality and patient's demographic characteristics, clinic and laboratory findings

	28 day mortality		
	Alive (n=46)	**Deceased (n=31)**	**p-values**
Sex; n (%)			
Male	27 (55.1%)	22 (44.9%)	0.272
Female	19 (67.9%)	9 (32.1%)	
Age (year)	71 (62-78)	75 (65-81)	0.134
SBP (mmHg)	100 (88.75-110)	80 (80-100)	**0.020**
DBP (mmHg)	60 (50-70)	50 (50-68)	0.217
Pulse rate (beats/min)	102.72±20.65	113.1±24.51	**0.049**
Body temperature (°C)	37.5 (36.78-38.35)	37.5 (36.5-38.6)	0.901
Respiratory rate	20 (17-26)	23 (20-30)	0.117
GCS	15 (14-15)	13 (10-15)	**<0.001**
WBC count (cells/mm^3)	16.35 (10.59-21.84)	11.68 (7.01-18)	**0.014**
Hemoglobin (mg/dL)	11.9±2.35	11.87±2.2	0.964
Platelet count (cells/mm^3)	179 (140.25-282.75)	190 (106-304)	0.827
Neutrophil count (cells/mm^3)	14.05±7.88	10.84±6.35	0.063
Lymphocyte count (cells/µL)	1.17 (0.65-2.04)	0.81 (0.38-1.2)	**0.029**
Monocyte count	0.95±0.6	0.55±0.33	**<0.001**
IGG	0.13 (0.06-0.27)	0.09 (0.03-0.19)	0.138
NLR	11.48 (4.43-21.25)	11.38 (7.58-18.84)	0.732
PLR	159.47 (100.05-263)	285.19 (101.67-447.96)	0.101
LMR	1.63 (0.79-2.75)	1.79 (1.02-3.14)	0.506
ALT (IU/L)	19 (10-29.25)	18 (11-28)	0.872
AST (IU/L)	23 (14-34.5)	23 (19-49)	0.339
CRP	133 (39.25-275)	125 (60-188)	0.516
pH	7.36±0.08	7.4±0.08	**0.025**
PCO_2	42.54±9.52	38.06±10.82	0.059
Bicarbonate	22.4 (20.15-26.3)	23.1 (21.2-28.4)	0.403
Lactate (mmol/L)	2.2 (1.55-3.275)	3.1 (2.1-4.9)	**0.005**
SI	1.1±0.31	1.34±0.42	**0.005**
LSI	2.88±1.72	5.02±3.12	**0.001**

Values are presented as mean ± SD, median (25^{th} and 75^{th} quartile), or n (%)
ALT: Alanine transaminoferase, AST: Aspartate transaminoferase, CRP: C-reactive protein, DBP: Diastolic blood pressure, GCS: Glasgow coma scale, IGG: Immature granulocytes, LMR: Lymphocyte-monocyte ratio, LSI: Lactate-shock index, NLR: Neutrophil-lymphocyte ratio, PCO_2: Partial pressure of carbon dioxide, PLR: Platelet-lymphocyte ratio, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells

28-day mortality. Shock index (OR: 9.623, 95% CI 1.358-68.16, p=0.023) and LSI (OR: 1.333, 95% CI 1.031-1.723, p=0.029) were identified as independent prognostic indicators of 28-day mortality. The analysis of multivariate logistic regression is shown in Table 2.

Receiver operating characteristics analysis was performed on all patients to predict 28-day mortality. Lactate shock index [area under the curve (AUC): 0.710] showed better performance than both SI (AUC: 0.690) and lactate (AUC: 0.681). The ROC curve graph is shown in Figure 1, and Table 3 contains statistics on the performance characteristics of the variables in predicting 28-day mortality.

Discussion

This study demonstrated that LSI, a combined index of lactate and SI, is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index (AUC: 0.710) performed better than lactate (AUC: 0.690) and SI (AUC: 0.681) in predicting 28-day mortality.

Sepsis is a significant public health problem worldwide, being one of the leading causes of hospital admission and death (16). In-hospital mortality due to sepsis occurs in approximately 20% of patients, with rates even higher in those with septic shock. Additionally, patients treated for sepsis remain at risk for mortality and morbidity after discharge (17). Due to this high mortality risk, identifying critically ill patients through risk stratification is crucial. Effective risk classification tools are needed to successfully predict patient outcomes in sepsis and guide treatment and management strategies in the initial hours (1,4).

Neutrophil-lymphocyte ratio, an inflammatory marker obtained by dividing the neutrophil count by the lymphocyte count, is an indicator of systemic inflammation (16). Sepsis is characterized by an inappropriate inflammatory response to infection by the host. Physiological stress due to sepsis causes an increase in neutrophil count while inducing lymphopenia by promoting lymphocyte apoptosis (18,19). However, neutrophil values may be normal or low in septic patients, limiting the prognostic value of neutrophil and lymphocyte counts. Studies have shown that NLR is more reliable than neutrophil and lymphocyte counts alone (20,21). Liu et al. (22) found that increasing NLR values predicted 28-day mortality in septic patients. Similarly, another study demonstrated that NLR is an independent predictor of 28-day mortality (18). In our study, we found that low lymphocyte count was associated with mortality, consistent with the literature. However, neutrophil count was lower in deceased patients compared to survivors, with no statistical relationship with mortality. This discrepancy may be due to the patient population and sample size included in the study. Consequently, the failure of NLR to predict mortality may be explained by the difference in neutrophil counts between deceased and surviving patients.

Shock index is a reliable indicator of hemodynamic status and has the advantage of being easily calculable at the bedside. It is a more sensitive indicator of hemodynamic status than HR and SBP alone (9). Previous studies have shown the success of SI in predicting adverse clinical outcomes in various conditions such as trauma, myocardial infarction, sepsis, and pneumonia (4,8,9,23). The inappropriate inflammatory response seen in sepsis leads to increased vascular permeability and suppression of vascular tone. This results in decreased arterial blood pressure and impaired tissue perfusion. Compensatory mechanisms activate the alpha and beta adrenergic systems, increasing HR and cardiac contractility (24). The hemodynamic effects of sepsis are associated with an increase in SI. Al Aseri et al. (10) found that SI was a successful predictor of hemodynamic collapse in septic patients, and similarly, Devendra Prasad et al. (9) showed that SI predicted the need for mechanical ventilation. Studies have also investigated the relationship between SI and short- and long-term mortality in septic patients (4). Zhang et al. (1) investigated the performance of SI in predicting 3-day and in-hospital mortality in patients with septic shock; they found an AUC of 0.746 for 3-day mortality and 0.654 for in-hospital mortality. Multivariate logistic regression analysis in the same study found SI to be an independent predictor of 3-day mortality (1). Another study investigating the prognostic performance of SI in

Table 2. ORs of the prognostic factors for predicting 28-day mortality in patients with sepsis

Parameters	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Lactate	1.707 (1.195-2.438)	**0.003**	1.712 (1.188-2.468)	**0.004**	1.467 (0.979-2.199)	0.064
SI	6.447 (1.568-26.51)	**0.010**	6.424 (1.467-28.138)	**0.014**	9.623 (1.358-68.16)	**0.023**
LSI	1.448 (1.157-1.814)	**0.001**	1.446 (1.151-1.816)	**0.002**	1.333 (1.031-1.723)	**0.029**

Model 1: Unadjusted model
Model 2: Adjusted for age and sex
Model 3: Each variable was adjusted for age, sex, GCS, WBC, lymphocyte and monocyte
CI: Confidence interval, GCS: Glasgow coma scale, LSI: Lactate-shock index, OR: Odds ratio, SI: Shock index, WBC: White blood cells, PPV: Positive predictive value, NPV: Negative predictive value

predicting 28-day mortality identified sensitivities of 0.71 and specificities of 0.41 for two different cut-off points (≥0.7 and ≥1.0) and a sensitivity of 0.37 and specificity of 0.80 for a cut-off point of >1.0 (25). Another study reported a sensitivity of 0.731, a specificity of 0.458 and an AUC of 0.708 for short-term mortality at an SI cut-off of ≥1.2 (8). In our study, consistent with previous studies, we found an AUC of 0.681, sensitivity of 0.71, and specificity of 0.652 in predicting 28-day mortality for an SI cut-off of ≥1.144. Logistic regression analysis demonstrated that SI is an independent predictor of 28-day mortality.

High lactate levels have been shown to be associated with increased mortality and adverse clinical outcomes in various conditions, including sepsis (15,26). Sepsis leads to increased lactate levels due to impaired tissue perfusion and cellular hypoxia (27). Current sepsis guidelines emphasize the central role of lactate levels in patient management (26,28). Filho et al. (29) investigated the relationship between initial lactate levels and mortality in septic patients, finding an AUC of 0.70, sensitivity of 0.674, and specificity of 0.617 for a cut-off of >2.5 in predicting 28-day mortality. Another study examining the performance of lactate in predicting 28-day mortality in elderly septic patients reported a cut-off value of >2.4 with an AUC of 0.618, a sensitivity of 0.483, and a specificity of 0.687 (28). Consistent with the literature, our study showed that increased lactate levels were associated with increased mortality. For predicting 28-day mortality, the AUC of lactate was 0.690, with a sensitivity of 0.71 and specificity of 0.63 at a cut-off of >2.65. We recommend a cut-off of 2.5 for lactate, in line with previous clinical studies (26,30), despite studies suggesting a cut-off of 4.0. Choosing a higher cut-off could lead to the misclassification of patients with moderate hyperlactatemia, who are at risk of morbidity and mortality, as low-risk, thus missing a patient group that could benefit from aggressive treatment and intensive monitoring (29).

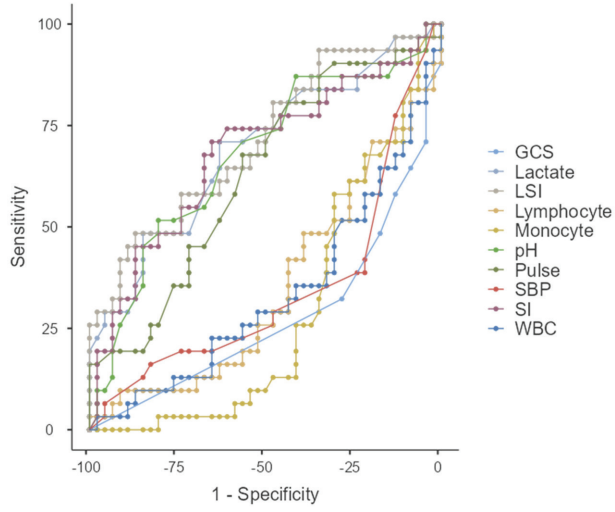

Figure 1. ROC curve analysis for predicting 28-days mortality
GCS: Glasgow coma scale, LSI: Lactate-shock index, ROC: Receiver operating characteristic, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells

Considering the performance of lactate and SI in predicting adverse outcomes, including mortality, in septic patients, we developed LSI. Lactate shock index is a practical, low-cost index obtained by multiplying lactate and SI and can be quickly calculated at the bedside. We compared the performance of this new index with the already established and proven performance of lactate and SI in predicting mortality in septic patients (1,8,25,28,29). In ROC curve analysis, LSI showed better performance in predicting 28-day mortality than lactate and SI (AUC 0.710 vs. 0.690 and 0.681, respectively). Additionally, LSI had the highest specificity (0.870) and PPV (0.720) among the predictors of 28-day mortality. Multivariate logistic regression analysis also identified LSI as an independent predictor of 28-day mortality in septic patients.

Table 3. Cut-off points and performance characteristics of prognostic factors in predicting 28-day mortality

Parameters	AUC	95% CI	Cut-off	Sensitivity	Specificity	PPV	NPV	p-value
SBP	0.656	(0.525-0.786)	83	0.613	0.783	0.66	0.75	0.021
Pulse rate	0.628	(0.501-0.755)	105	0.677	0.565	0.51	0.72	0.049
GCS	0.723	(0.603-0.843)	14.5	0.677	0.717	0.62	0.77	0.001
WBC	0.666	(0.541-0.791)	12.325	0.645	0.674	0.57	0.74	0.014
Lymphocyte	0.647	(0.521-0.773)	1.28	0.806	0.478	0.51	0.79	0.029
Monocyte	0.713	(0.599-0.827)	0.835	0.871	0.587	0.59	0.87	0.002
pH	0.673	(0.547-0.798)	7.415	0.516	0.804	0.64	0.71	0.011
Lactate	0.690	(0.567-0.813)	2.65	0.71	0.63	0.56	0.76	0.005
SI	0.681	(0.555-0.808)	1.144	0.71	0.652	0.58	0.77	0.007
LSI	0.710	(0.591-0.83)	5.236	0.484	0.870	0.72	0.71	0.002

AUC: Area under the curve, CI: Confidence interval, GCS: Glasgow coma scale, LR: Likehood ratio, LSI: Lactate-shock index, SBP: Systolic blood pressure, SI: Shock index, WBC: White blood cells, PPV: Positive predictive value, NPV: Negative predictive value

Study Limitations

This study has several limitations. The study was conducted at a single center, and the small number of patients included constitutes the main limitation. This affects the generalizability of the study results.

Conclusion

This study demonstrates that LSI is an independent predictor of 28-day mortality in patients with sepsis. Lactate shock index showed better performance than both lactate and SI in predicting 28-day mortality. The findings suggest that LSI could be a valuable tool for early risk stratification of sepsis patients in the ED due to its superior prognostic performance. Incorporating LSI into clinical practice could facilitate the timely implementation of appropriate therapeutic interventions, thereby improving the clinical outcomes of patients with sepsis. Multicenter studies with larger patient cohorts are needed to validate the utility of LSI in different clinical settings.

Ethics

Ethics Committee Approval: This study was conducted prospectively in the ED of a tertiary hospital following approval from the Ordu University Clinical Research Ethics Committee (approval no.: 2023/41, date: 03.02.2023).

Informed Consent: Written and verbal consent was obtained from the participants.

Footnotes

Authorship Contributions

Concept: I.C., A.A., Design: I.C., A.A., A.K., Data Collection or Processing: A.K., M.T., Analysis or Interpretation: I.C., M.S.S., Literature Search: I.C., M.S.S., M.T., Writing: I.C., A.A., A.K., M.S.S., M.T.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Investigation of Clonal Relationship Between *Candida Parapsilosis* and *Candida Glabrata* Strains Isolated from Blood Culture by Pulse Field Gel Electrophoresis

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Abstract

Aim: Candidemia may occur when endogenous *Candida* species in the intestinal microbiota enter the bloodstream in patients with risk factors. Apart from endogenous transmission, patients can also transmit it exogenously. In the current study, we aimed to investigate the fluconazole susceptibility and genotypes of *Candida parapsilosis* (*C.parapsilosis*) and *Candida glabrata* (*C. glabrata*) strains that cause candidemia.

Methods: Twenty-six *C. parapsilosis* and sixteen *C. glabrata* strains were included in the study. Fluconazole sensitivity was determined by the broth microdilution method. Genotyping of strains was done by pulsed-field gel electrophoresis.

Results: Nine (34%) of *C. parapsilosis* strains and 3 (19%) of *C. glabrata* strains were found to be resistant to fluconazole. Among 26 *C. parapsilosis* isolates, 17 different genotypes were detected and clustered isolates were collected in five clusters. Fourteen out of the 26 *C. parapsilosis* isolates are placed in one of the clusters, with a clustering rate of 53.8%. Among 16 *C. glabrata* isolates, 11 different genotypes were detected and divided into four clusters. Nine out of the 16 *C. glabrata* isolates are placed in one of the clusters, with a clustering rate of 56.2%.

Conclusion: Our data indicated the possibility of nosocomial transmission of *C. parapsilosis* and *C. glabrata* among intensive care unit patients in our hospital. Infection control policies should be strictly applied in our hospital to prevent cross-transmission.

Keywords: *Candida parapsilosis*, *Candida glabrata*, fluconazole susceptibility, genotype

Introduction

Bloodstream infections caused by *Candida* are less common than those caused by other pathogens. They are seen especially in patients who have undergone surgery, those in intensive care for long periods, those who are cancer patients, and immunocompromised patients who have undergone allogeneic stem cell transplantation. *Candida* species are isolated from 4.5% of hospital-acquired bloodstream infections (1). Among *Candida* spp., *Candida albicans* (*C. albicans*) is the most common species worldwide, although recently non-albicans *Candida* species have been reported to be more common (2). Additionally, the incidence of non-albicans *Candida* species varies from region to region. While *Candida parapsilosis (C. parapsilosis)* is more common in Asia (including Japan and China), Latin America (including Brazil), and Southern Europe, *C. glabrata* is more common in the United States, Australia, and Northern Europe (3).

Candida parapsilosis strains can spread more easily in hospitals than other *Candida* species because they can stick to surfaces, attach to the hands of healthcare workers and medical devices, and last on surfaces for up to 28 days.

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Some studies have shown that *C. parapsilosis* strains have high minimal inhibitory concentrations for echinocandin drugs due to naturally occurring FKS1 polymorphism. Additionally, very high azole resistance rates have been reported in some regions. This makes it difficult to choose empiric antifungal drug treatment in *C. parapsilosis* infections (4-7). Recently, the rate of isolation of *Candida glabrata* (*C. glabrata*) from bloodstream infections has been increasing. *Candida glabrata* is isolated from 18-25% of candidemia cases in North America. It is the second most common *Candida* species causing candidemia. In addition, *C. glabrata* is the main bloodstream fungal pathogen in patients with hematological malignancies. Azole group antifungals are frequently used for prophylaxis and treatment of candidemia. As a result, azole resistance is gradually increasing among *C. glabrata* isolates. While the azole resistance rate of *C. glabrata* strains worldwide is around 8%, in some centers, this rate exceeds 20% (8,9).

Candidemia can happen when *Candida* species that normally live in the intestines get into the bloodstream of patients who have certain risk factors like cancer, long stays in intensive care, or long-term use of antibiotics. In addition to endogenous transmission, it can also be transmitted exogenously from patient to patient. Genotyping can help clarify potential *Candida* outbreaks in hospitalized patients and whether exogenous transmission is occurring (10).

We hypothesized that there is a link between fluconazole resistance and genotypes in *C. parapsilosis* and *C. glabrata* strains. We aimed to investigate the fluconazole susceptibility and genotypes of *C. parapsilosis* and *C. glabrata* strains that cause candidemia. Additionally, it was investigated whether there was clustering among genotypes. This will contribute to the strict implementation of infection control policies such as hand washing, using protective equipment, and staff training to prevent cross-contamination in hospitals and to antimicrobial resistance surveillance to prevent the spread of resistant isolates.

Materials and Methods

Compliance with Ethical Standards

For the study, ethics committee approval was obtained from the Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 23-KAEK-027, date: 16.02.2023). Written consent was obtained from all participants, and the study complied with the Declaration of Helsinki.

Study Design

It is a cross-sectional study that included *C. parapsilosis* and *C. glabrata* strains causing candidemia between November 2019 and September 2021. Firstly, identification of strains isolated from blood culture was performed, and antifungal susceptibility tests were performed. Identification of *Candida* strains was performed with the YST8 diagnostic panel (Diagnostics, Slovenia), using their characteristic appearance in cornmeal Tween-80 (Himedia, India) medium and the Vitek II automatic device (bioMérieux, France). Fluconazole sensitivity was determined by the broth microdilution method (Sigma Aldrich, St. Louis, MO, USA) and interpreted using Clinical and Laboratory Standards Institute M27-A Supplement 4 clinical breakpoints. *Candida* krusei American Type Culture Collection (ATCC) 6258 and *C. parapsilosis* (ATCC 22019) were used as quality control strains.

Then, the genotypes of the strains were determined by pulse-field gel electrophoresis. Electrophoretic karyotyping for discrimination of isolates was performed as previously described in the literature with minor modifications (11,12). Electrophoresis was performed in 0.5×TBE buffer using the contour-clamped homogeneous electric field method with a Contour-Clamped Homogeneous Electric Field DRII system (Bio-Rad, Richmond, USA). The electrophoresis conditions were 12°C at 6 V/cm² for 48 hours. The initial and final switch times were 90 seconds and 360 seconds, respectively. For all methods, each gel was stained with ethidium bromide (5 mg/mL) and destained in tap water and then viewed and photographed under ultraviolet light.

Analysis of arbitrarily primed polymerase chain reaction band profiles was performed with the GelCompar software package (version 6.5; Applied Maths, Sint-Martens-Latem, Belgium). The Dice correlation coefficient was used for similarity calculations for band analysis, and the unweighted pair group method with arithmetic mean was used for clustering analysis. If the Dice similarity coefficient value was below 95%, isolates were identified as different genotypes.

Statistical Analysis

Statistical analysis of the data was performed with IBM SPSS Statistics version 20 (IBM, USA). Whether the numerical data were normally distributed was evaluated with the Shapiro-Wilk test. The expression of normally distributed data is "mean ± standard deviation", and the expression of non-normally distributed data is "median (25^{th} percentile-75^{th} percentile)." Student's t-test was used to compare numerical data that followed a normal distribution, and the Mann-Whitney U test was used to compare numerical data that did not follow a normal distribution. To compare qualitative data, the chi-square test was used. When more than 20% of cells had expected frequencies <5, Fisher's exact test was used.

Results

While the number of *C. parapsilosis* that caused candidemia between November 2019 and September 2021 was 26, the number of *C. glabrata* was 16. The median age of the patients with *C. parapsilosis* was found to be 74 years (65-83). The median age of the patients with

C. glabrata was 65 years (56-74). The median age of the patients with *C. parapsilosis* was significantly higher than that of patients with *C. glabrata* (p=0.036). Twenty-five (96%) of the patients with *C. parapsilosis* were receiving treatment in intensive care, and 1 (4%) in the oncology service. 14 (88%) of the patients with *C. glabrata* were receiving treatment in the intensive care unit (ICU) and 2 (12%) in the oncology service (Table 1).

Of the *C. parapsilosis* strains, 13 (50%) were susceptible to fluconazole, 4 (15%) were dose-dependent susceptible, and 9 (35%) were resistant. Of the *C. glabrata* strains, 13 (81%) were susceptible in a dose-dependent manner to fluconazole, and 3 (19%) were resistant. The minimum inhibitory concentration (MIC) range, MIC_{50}, MIC_{90}, and geometric mean values of the strains are given in Table 2.

Among 26 *C. parapsilosis* isolates, 17 different genotypes were detected, which were collected into five clusters (tolerance 1.0, optimization 3.0, cut-off 95%). Fourteen out of the 26 *C. parapsilosis* isolates are placed in one of the clusters, with a clustering rate of 53.8%. The largest cluster is genotype 1 with four isolates. It is followed by genotype 8, and genotype 13 clusters with three isolates, while genotype 7 and genotype 9 cluster with two isolates. (Figure 1)

Table 1. Age, gender, median length of hospital stays and accompanying diseases of the patients

	***C. parapsilosis* (n=26)**	***C. glabrata* (n=16)**	**p-value**
Gender Male Female	 17(65%) 9 (35%)	 9 (56%) 7 (44%)	 0.553[1]
Age (year)	74 (65-83)	65 (56-74)	0.036[2]
Median length of hospital stays (days)	35 (21-80)	28 (19-35)	0.109[1]
Malignancy (%)	8 (31%)	5 (31%)	0.973[2]
Hypertension (%)	6 (23%)	3 (19%)	13
Cardiovascular disease (%)	3 (12%)	6 (38%)	0.062[3]
Lung disease (%)	2 (8%)	0 (0%)	0.516[3]
Diabetes mellitus (%)	2 (8%)	0 (0%)	0.516[3]

Mann-Whitney U test was used, chi-square test was used, Fisher's exact test was used
C.: Candida
[1]: Mann Whitney U test was used
[2]: Chi-square test was used
[3]: Fisher Exact test was used

Among 16 *C. glabrata* isolates, 11 different genotypes were detected. The clustered isolates were collected into four clusters (tolerance 1.0, optimization 3.0, cut-off 95%). 9 out of the 16 *C. glabrata* isolates are placed in one of the clusters, with a clustering rate of 56.2%. The largest cluster is the genotype 1 with three isolates. It is followed by genotype 5, genotype 6, and genotype 7, each forming clusters with two isolates (Figure 2).

Discussion

Long ICU stays, long-term systemic antibiotic use, underlying immunosuppressive diseases, and old age are the main candidemia risk factors (1). In this study, 96% of the patients isolated with *C. parapsilosis* and 88% of the patients isolated with *C. glabrata* were in the ICU. The number of patients over 60 years of age with isolated *C. parapsilosis* was 21 (81%). It was found to be 11 (69%) in *C. glabrata* patients. Various studies, similar to our study (13-15), have reported that *Candida* infections are more common in older patients, those in intensive care, and those with underlying diseases. It is known that the incidence of *C. parapsilosis* strains decreases with age, while the incidence of *C. glabrata* strains increases with age (16). However, in the current study, the median age of the patients with *C. parapsilosis* was significantly higher than that of patients with *C. glabrata* (p=0.036). The reason for this different result may be because of the examination of a certain period and the limited number of patients.

Antifungal resistance is a major problem in the treatment of candidemia. Fluconazole is usually used in the treatment of candidemia as well as other invasive *Candida* infections (17). Although *C. parapsilosis* isolates are usually reported as susceptible to fluconazole, recent studies have documented an increase in fluconazole-resistant *C. parapsilosis* isolates (18). Pfaller et al. (19), in their study examining the activity of fluconazole against 20.788 invasive *Candida* spp. isolates collected from 39 countries between 1997 and 2016, reported that 3.9% of *C. parapsilosis* isolates were resistant to fluconazole. The rate of fluconazole resistance was reported as 26.4% in *C. parapsilosis* isolates in a recent study from our country. In the current study, 35% of *C. parasilosis* isolates were found to be resistant to fluconazole. However, in a study published by Caggiano et al. (20) in 2024, the fluconazole

Table 2. MIC range, MIC_{50}, MIC_{90} and Geometric mean values of *C. parapsilosis* and *C. glabrata* strains

	MIC range	**MIC_{50}**	**MIC_{90}**	**Geometric mean**
C. parapsilosis (n=26)	0.25->256	2	16	2.75
C. glabrata (n=16)	8->256	8	>256	17.44

C.: Candida, MIC: Minimum inhibitory concentration

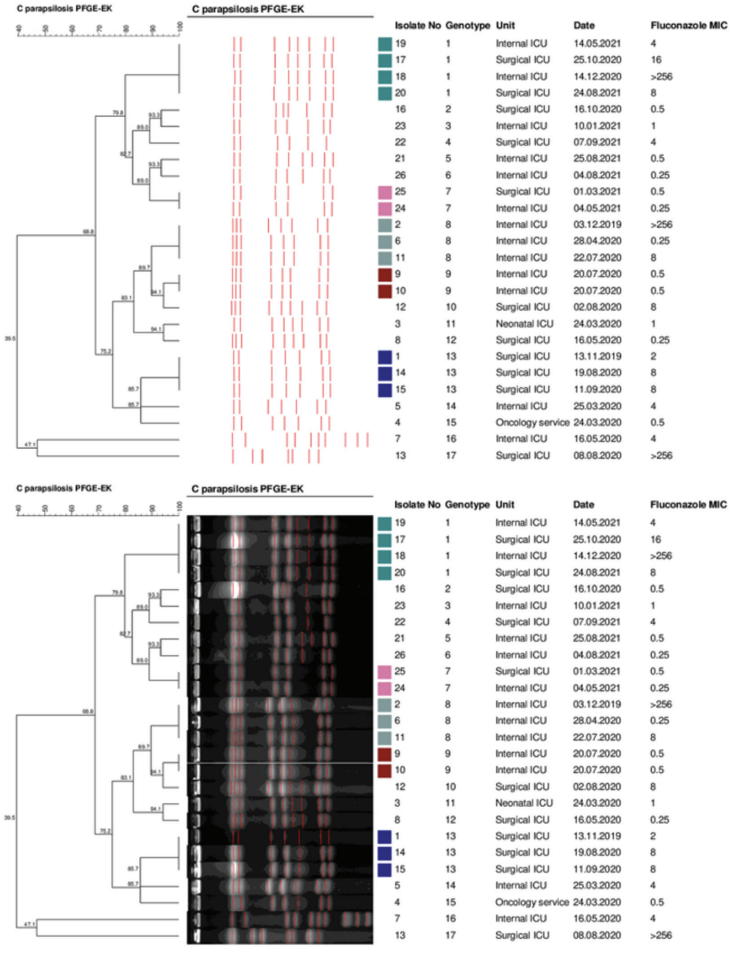

Figure 1. Dendogram showing clustering of *C. parapsilosis* strains
ICU: Intensive care unit, C.: Candida, PFGE: Pulsed-field gel electrophoresis MIC: Minimum inhibitory concentration

resistance rate in *C. parapsilosis* strains was reported as 82%. In the study by Misas et al. (4), while the fluconazole resistance rate of *C. parapsilosis* strains was found to be 17% in 2020, this rate became 34% in 2021. All these results show that the fluconazole resistance rate of *C. parapsilosis* strains has been increasing recently. This makes empirical drug selection and treatment of these strains quite difficult.

In a review study conducted by Beardsley et al., (21) fluconazole resistance rates in *C. glabrata* strains were found to range from 0% to 48% in 52 studies. In 16 of these, the fluconazole resistance rate was found to be above 10% (21). Castanheira et al. (22) have collected 1846 bloodstream isolates from 31 countries. They have documented that 11.9% of *C. glabrata* isolates were resistant to fluconazole. Yu et al. (13) reported a 6% fluconazole resistance rate in *C. glabrata* strains causing bloodstream infections. In this study, 81% of *C. glabrata* isolates were susceptible-dose dependent (S-DD) to fluconazole, while 19% were resistant. The incidence of *C. glabrata* strains and resistance rates to azole-echinocandin antifungals used in first-line therapy are increasing worldwide. Strategies need to be evaluated and implemented to prevent infection from occurring.

Candidemia mostly originates from endogenous *Candida* spp., but it can also be acquired. The pulsed-field gel electrophoresis (PFGE) plays an important role in tracking the source of candidemia, differentiating isolates, and conducting epidemiological investigations (23). In this study, we used PFGE to investigate the genetic relatedness among both the *C. parapsilosis* and *C. glabrata* isolates from candidemia.

Pulsed-field gel electrophoresis results of 26 *C. parapsilosis* isolates revealed the presence of 17 different genotypes. Fourteen of the 26 *C. parapsilosis* isolates were grouped into 5 clusters and one major group. All clustered isolates are from ICU patients. The largest cluster includes genotype 1, with 4 isolates. Three of these genotype 1 isolates were fluconazole resistant, while the other one was S-DD. The fact that all of these patients were treated

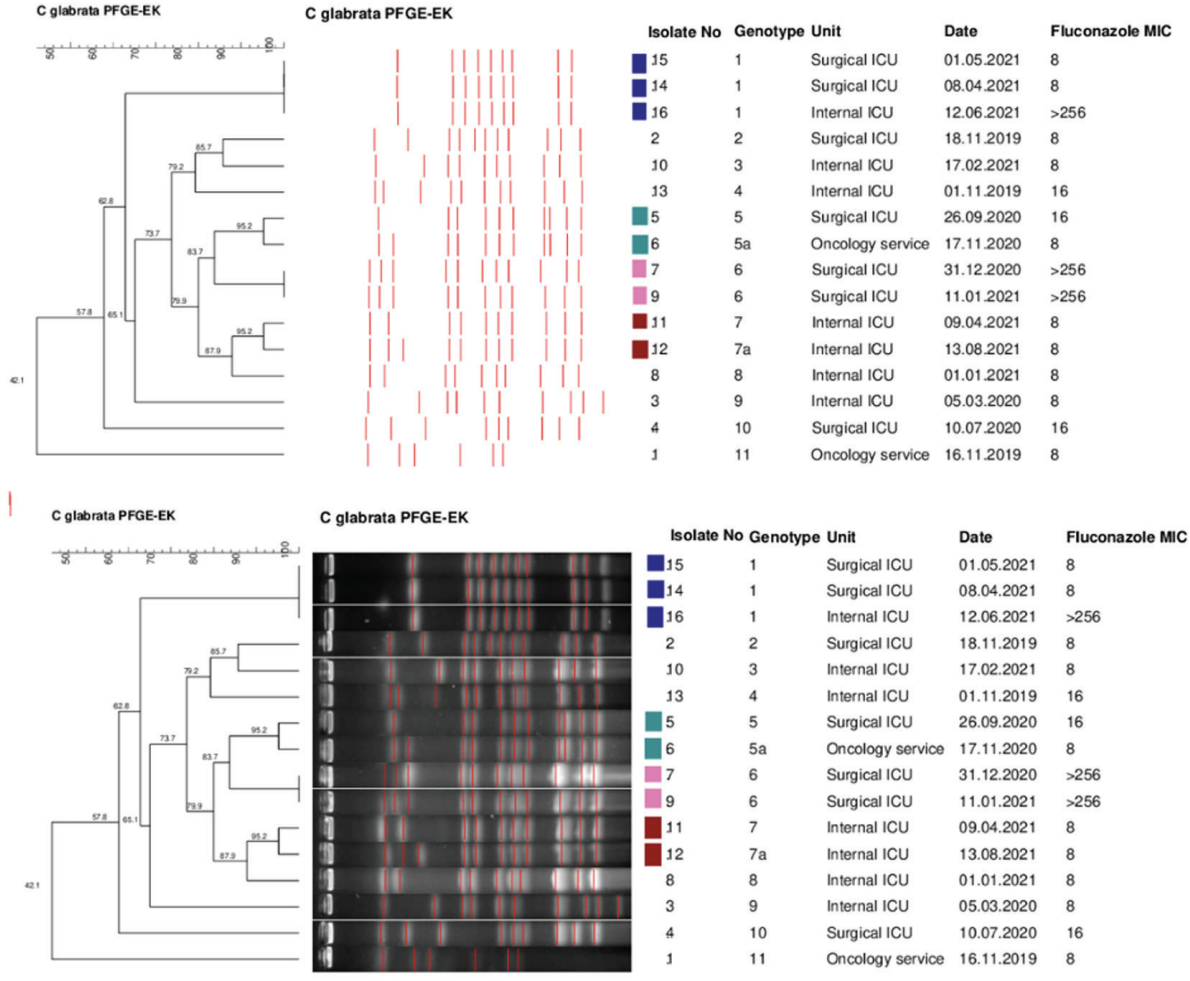

Figure 2. Dendogram showing clustering of *C. glabrata* strains
ICU: Intensive care unit, C.: Candida, PFGE: Pulsed-field gel electrophoresis, MIC: Minimum inhibitory concentration

in the same ICU and none of them were susceptible to fluconazole suggested that these strains originated from the same source. Pulcrano et al. (24) have analyzed 19 strains of *C. parapsilosis* isolated from the blood cultures of neonates by PFGE. They have reported a high degree of relatedness between the isolates. In their study, in which Caggiano et al. (20) examined 50 *C. parapsilosis* strains phylogenetically, it was found that fluconazole-resistant strains were similar to environmental strains. It was concluded that these strains may have been transmitted from the hospital environment. Another remarkable result was that all patients in genotype 13, the second largest cluster with 3 patients, had malignancy. In addition, the patients in this cluster were in the same ICU. Results suggest that these strains may have been transmitted from patient to patient within the hospital.

Pulsed-field gel electrophoresis results indicated that 9 of 16 *C. glabrata* isolates were clonally related with a clustering rate of 56.2%. All these isolates were recovered from the ICU except one. Two of the three fluconazole-resistant *C. glabrata* isolates belonged to genotype 6. Hwang et al. (8) examined 79 *C. glabrata* strains that caused infection in blood and found two different clusters in the same hospital. Similar to our study, they revealed that these strains were transmitted between patients treated within the hospital setting.

Study Limitations

The limitations of the current study are that the number of strains examined is small. This is because the study covers strains that grow within a certain period of time. Additionally, susceptibility testing could only be performed for fluconazole. Sensitivity testing against other antifungal drugs could not be performed. Despite these limitations, determining the genotypes of *Candida* strains and finding a cluster among them are the strengths of our study.

Conclusion

Our data indicated the possibility of nosocomial transmission of *C. parapsilosis* and *C. glabrata* among ICU patients in our hospital. Infection control policies such as hand washing, use of protective equipment, and personnel training should be strictly applied in our hospital to prevent cross-transmission. Antimicrobial resistance surveillance is crucial to prevent the spread of resistant isolates.

Ethics

Ethics Committee Approval: The study, ethics committee approval was obtained from Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 23-KAEK-027, date: 16.02.2023)

Informed Consent: Written consent was obtained from all participants and the study complied with the human rights declaration.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S.T., Concept: A.A., G.Y., Design: A.A., G.Y., B.O., Data Collection or Processing: E.S.T., Analysis or Interpretation: E.S.T., G.Y., B.O., Literature Search: A.A., G.Y., Writing: A.A., G.Y.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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The Relationship Between Hypothyroidism and Stress Urinary Incontinence: A Prospective Controlled Study

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Abstract

Aim: Thyroid hormones play a vital role in the regulation of multiple physiological systems, including the genitourinary system. We aimed to evaluate the relationship between thyroid hormone deficiency, which affects nearly all organs and systems, and stress urinary incontinence (SUI).

Methods: This prospective controlled study included patients with hypothyroidism, subclinical hypothyroidism, and a healthy control group. Demographic data and clinical characteristics such as the presence of, menopausal status, and number of vaginal deliveries were compared. Additionally, risk factors for stress incontinence were analyzed using multivariate analysis.

Results: Of the 65 patients included in the study, 21 were in the hypothyroid group, 16 were in the subclinical hypothyroid group, and 28 were in the control group. A statistically significant difference in the prevalence of SUI was observed only between the hypothyroid group and the control group. There was no significant difference in the severity of SUI between the groups.

Conclusion: Stress urinary incontinence is more common in patients with hypothyroidism compared to those with normal thyroid function. Elevated thyroid-stimulating hormone levels, menopausal status, and a higher number of vaginal deliveries are identified as risk factors for SUI.

Keywords: Hypothyroidism, thyroid hormones, female, urinary ıncontinence, delivery

Introduction

Hypothyroidism is a common endocrine disorder, with a reported prevalence ranging from 0.2% to 5.3% (1). It is approximately ten times more prevalent in women (2,3). The condition can adversely affect multiple organ systems, including the cardiovascular, musculoskeletal, endocrine, gastrointestinal, and neurocognitive systems (4-6).

Normal bladder function is maintained through the coordinated interplay of the nervous system, pelvic floor muscles, the urethrovesical angle, and the detrusor muscle. Disruptions in these components may impair bladder function and lead to the development of a variety of symptoms, including urinary incontinence. Neuropathy is among the neurological manifestations of hypothyroidism, and it may often present alongside other systemic symptoms (7,8). In this respect, voiding dysfunction may be related to hypothyroidism.

Thyroid hormones are among the most important for maintaining homeostasis. It is also an essential hormone for the proper functioning of the nervous system, which is crucial for bladder function. We hypothesized that low levels of this essential hormone may be related to stress urinary incontinence (SUI). Therefore, the aim of this study was to evaluate the relationship between hypothyroidism and SUI.

Materials and Methods

Compliance with Ethical Standards

The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences

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Turkey, Basaksehir Cam and Sakura City Hospital (approval no.: KAEK/2023.02.61, date: 13.03.2023). Written informed consent was obtained from all participants.

Study Design

We prospectively analyzed patients who were admitted to the internal medicine department between June 2023 and June 2024. Three groups were formed from these patients as follows: those newly diagnosed with hypothyroidism, those newly diagnosed with subclinical hypothyroidism, and healthy individuals. Patients with hypothyroidism were defined as having elevated thyroid stimulating hormone (TSH) and low free T4 levels, while patients with subclinical hypothyroidism were defined as having high TSH and normal free T4 levels.

Patients with a previous diagnosis of hypothyroidism or those currently using thyroid-related medications were excluded. In addition, patients with a history of surgery, medication use associated with urinary incontinence, and those who declined to participate in the study were excluded. The flowchart of enrolled patients is presented in Figure 1.

Demographic characteristics, educational status, history of abortion, hysterectomy, menopausal status, and SUI status of all patients were recorded prospectively. Additionally, the severity of SUI was measured with the incontinence severity index (9). Intergroup comparisons were conducted and factors associated with stress incontinence were evaluated.

Statistical Analysis

Statistical results were analyzed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). All continuous variables were stated as mean ± standard deviation. The normal distribution of the variables was tested with the Shapiro-Wilk test. The chi-squared test and the Kruskal-Wallis test were used for assessment of differences between groups. Multivariate and univariate logistic regression analyses were performed to explore parameters associated with SUI. P-value <0.05 was accepted as statistically significant.

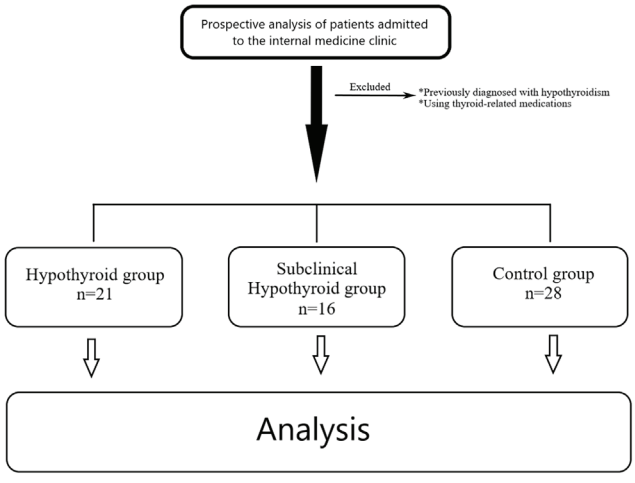

Figure 1. The flowchart of enrolled patients

Results

A total of 65 patients were included in the study. Of these, 21 (32%) were in the hypothyroid group, 16 (25%) were in the subclinical hypothyroid group, and 28 (43%) patients were in the control group.

The demographic data and general characteristics of all patients are presented in Table 1. The mean age of the patients was 59.8±14.5 years, 53.7±2.2 years, and 55±9.1 years in the control group, hypothyroid group, and subclinical hypothyroid group, respectively (p=0.210). The mean body mass index of patients was 27.6±5.6 in the control group, 30.2±4.5 in the hypothyroid group, and 30.5±5.7 in the subclinical hypothyroid group (p=0.121).

The mean number of natural vaginal deliveries per patient was 1.96±1.7 in the control group, 1.81±1.4 in the hypothyroid group, and 1.75±1.5 in the subclinical hypothyroid group (p=0.937). Stress urinary incontinence was observed in 2 patients in the control group, 6 patients in the hypothyroid group, and 4 patients in the subclinical hypothyroid group. There was a statistically significant difference between the control group and the hypothyroid group (p=0.012). There was no statistically significant difference in the severity of SUI between the groups (p=0.287).

According to univariate and multivariate analysis, TSH levels, the number of natural vaginal deliveries, and menopause were found to be risk factors for SUI (Table 2).

Discussion

Hypothyroidism is a clinical syndrome resulting from thyroid hormone deficiency, affecting nearly all systems in the body. Thyroid stimulating hormone, secreted by the pituitary gland, has been shown to affect striated and smooth muscles, blood vessels, bone fibroblasts, and glomerular filtration (10-12). Given that these structures are distributed throughout the body, it is not surprising that hypothyroidism has widespread systemic effects. On the other hand, stress incontinence can be defined as the involuntary leakage of urine during activities that increase intra-abdominal pressure, such as laughing, coughing, sneezing, lifting heavy objects, or exercising. Stress urinary incontinence is a bothersome disease that negatively affects the social and sexual lives of patients (13,14). In this study, which explored the relationship between these two clinically significant conditions, we observed a higher prevalence of SUI among patients with hypothyroidism.

Hypothyroidism has previously been examined in the literature as a potential contributing factor to urinary system disorders. Urinary retention cases due to hypothyroidism have been reported. Additionally, cases of paralytic ileus associated with bladder atony in hypothyroidism have been reported (15,16). Vahdatpour et al. (17) investigated potential risk factors associated with SUI in their study. Similar to our study, they found that there is a direct relationship between SUI and hypothyroidism. In contrast, Demir et al. (18) in a cohort study, found no statistically significant relationship between SUI and hypothyroidism.

Various factors may play a role in the development of

Table 1. General characteristics of all patients

	Control n=28	**Hypothyroid n=21**	**Subclinical hypothyroidism n=16**	**p-value**
Age (Mean ± SD)	59.8±14.5	53.7±2.2	55±9.1	0.210 (Ψ)
BMI (kg/m^2) (Mean ± SD)	27.6±5.6	30.2±4.5	30.5±5.7	0.121 (Ψ)
Educational level				
Illiterate Qualified Highly qualified	5 18 5	3 14 4	2 11 3	0.993 (χ^2)
Diabetes mellitus (Yes/No)	4/24	4/17	3/13	0.839 (χ^2)
Pelvic organs prolapse (Yes/No)	1/27	0/21	1/15	0.717 (χ^2)
Hysterectomy (Yes/No)	8/20	7/14	3/13	0.638 (χ^2)
Menopause (Yes/No)	22/6	12/9	10/6	0.289 (χ^2)
Abortion (Yes/No)	2/26	2/19	1/15	0.924 (χ^2)
Natural vaginal delivery number (Mean ± SD)	1.96±1.7	1.81±1.4	1.75±1.5	0.937 (Ψ)
SUI status (Yes/No)	2/26 Φ Ω	6/15 Φ λ	4/12 λ Ω	**0.025 (χ^2)** (Φ0.012) (λ0.491) (Ω0.169)
Severity of SUI				
No Slight Moderate Severe Very severe	26 0 1 1 0	15 2 3 1 0	12 2 1 1 0	0.287 (χ^2)

χ^2: Chi-squared test, Ψ: Kruskal-Wallis test, Φ: Comparing hypothyroid and control groups, λ: Comparing hypothyroid and subclinical hypothyroid groups, Ω: Comparing subclinical hypothyroid and control groups
SD: Standard deviation, SUI: Stress urinary incontinence

Table 2. Univariate and multivariate regression models to predict stress urinary incontinence

	Univarite Model			**Multivarite Model**		
		95% CI			**95% CI**	
	OR	**Lower-upper**	**p-value**	**OR**	**Lower-upper**	**p-value**
Age	1.23	1.052-1.448	0.059			
BMI	1.19	0.929-1.525	0.158			
TSH	2.07	1.344-3.195	**<0.001**	3.02	1.031 - 8.863	**0.04**
T4	0.22	0.015-3.458	0.286			
Natural vaginal delivery number	10.61	1.154-9.541	**<0.001**	10.34	1.193 - 27.078	**0.03**
Diabetes status	1.16	0.132-3.126	0.583			
POP status	0.40	0.008-3.021	0.222			
Hysterectomy history	2.80	0.252-4.805	0.899			
Abortion history	1.62	0.002-0.715	0.981			
Menopause status	0.05	0.004-0.564	**0.015**	0.08	0.009 - 0.695	**0.02**
Education status	4.93	0.688-35.367	0.068			

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, TSH: Thyroid stimulating hormone, POP: Pelvic organ prolapse

SUI, including weakened pelvic floor muscle contractions, strenuous exercise and physical activities, aging, menopause, number and mode of delivery, weight gain, constipation, chronic cough, and many others (19,20). In our multivariate analysis, we found that an increased number of vaginal deliveries and postmenopausal status are risk factors for SUI consistent with the literature. Hypothyroidism may contribute to muscle weakness, including dysfunction of the pelvic floor muscles. It can also cause a slowdown in metabolism, resulting in weight gain and increased abdominal fat, which can elevate intra-abdominal pressure on both the pelvic floor and the bladder.

In a recent study conducted by Zargham et al. (21) a higher prevalence of SUI was observed in patients with hypothyroidism, similar to our study. Similarly, they did not find a significant association regarding the severity of stress incontinence. The relationship between hypothyroidism and the development of muscle weakness may be related to changes in muscle structure. In an animal study, Sánchez-García et al. (22) demonstrated that hypothyroidism might cause the phenotypic shift in muscle fiber type from fast-twitch (type II) to slow-twitch (type I) fibers, promoting muscle weakness in female rabbits. Since the urethral sphincteric complex and the pelvic floor need to be rich in fast-twitch muscle fibers to prevent SUI when intra-abdominal pressure increases, hypothyroidism may be a contributing factor to SUI.

To the best of our knowledge, there are few studies in the literature that have evaluated SUI in patients stratified by the presence of hypothyroidism or subclinical hypothyroidism. Although we observed an increase in SUI in subclinical hypothyroidism, which is a mild form of hypothyroidism, we did not find a statistically significant difference.

Study Limitations

The present study is not without limitations. Our study includes a small number of patients. We did not use a validated questionnaire, such as the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms. The post-treatment period for hypothyroidism has not been monitored to assess how SUI affects the condition. Despite these limitations, the subgroup analysis of hypothyroid patients in terms of stress incontinence and the prospective controlled nature of the study can be considered strengths of the study. prospective studies can be designed to investigate this subject.

Conclusion

Patients with hypothyroidism appear to represent a high-risk group for SUI. Elevated TSH levels, menopause, and a greater number of vaginal deliveries have been identified as significant risk factors. A clearer understanding of the relationship between hypothyroidism and SUI may offer valuable insights for developing more targeted treatment strategies.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital (approval no.: KAEK/2023.02.61, date: 13.03.2023).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.C., Concept: O.C., Design: B.C., O.C., Data Collection or Processing: B.C., Analysis or Interpretation: B.C., O.C., Literature Search: B.C., Writing: B.C., O.C.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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The Impact of Attention-deficit/Hyperactivity Disorder Assessments on Predicting Occupational Foreign Body Penetration Injuries

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Abstract

Aim: Our hypothesis was that individuals who suffer from penetrating foreign body injuries from work-related accidents are more likely to exhibit attention deficit hyperactivity disorder (ADHD) symptoms than those without such a history. The purpose of this study was to reveal whether there is a difference in ADHD diagnosis between patients who suffered penetrating foreign body injuries in a work accident and health volunteers who have not had a work accident before.

Methods: This study was designed as a retrospective, controlled, comparative study. Between January 2023 and December 2023, 47 patients who underwent surgery due to penetrating foreign body injury and 48 control group patients who were actively working and had no previous penetrating foreign body injury were included in the study. Attention deficit and hyperactivity disorder in patients was evaluated with the adult ADHD self-report scale version 1.1 (ASRS-v1.1) test administered by a specialist psychiatrist.

Results: The study included 95 patients-42 women and 53 men, with an average age of 35.1±11.5 in the patient group and 38.4±13.5 in the control group. When attention deficit subtype scores and ASRS-v1.1 total scores were examined, a statistically significant difference was found such that the patient group had higher scores than the control group in all three scoring systems.

Conclusion: This retrospective randomized controlled study set forth a broader perspective on a frequently seen trauma in the orthopedic emergency department. The ASRS-v1.1 test can be used as a tool to prevent further work-related accidents in work groups that use sharp objects and require maintaining attention.

Keywords: ASRS-v1.1, attention deficiency and hyperactivity disorder, foreign body injury, work accident

Introduction

Penetrating foreign body injuries constitute a significant portion of cases in emergency orthopedic trauma; by definition, they cover the events in which foreign objects penetrate the tissues (1,2). Accidents resulting in foreign object penetration injuries particularly involve workers in industries involving textiles, construction, manufacturing, or agriculture (2). Workers in these areas may be exposed to sharp tools, machinery, or objects that can cause penetrating injuries (3). These injuries can bring various complications, such as infection and foreign body retention in the body, and in some cases, penetrating injuries can even damage nerves, vessels, and internal organs; therefore, careful examination and appropriate intervention are required to minimize such complications (4-8). Prevention can be achieved by taking additional

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safety measures in environments and for individuals that may be prone to such accidents (9).

Attention deficit hyperactivity disorder (ADHD) is a pathological condition characterized by symptoms such as difficulty paying attention, difficulty in impulse control, and poor organizational skills; in addition, it is usually diagnosed in childhood (10,11). Attention deficit hyperactivity disorder can affect a person's ability to maintain attention, follow instructions, and anticipate dangers at work. Work accidents may occur as a result of carelessness due to distraction or hyperactivity (12,13). Making quick decisions, taking actions without thinking, and ignoring risky situations can lead to accidents (11).

The purpose of this study was to reveal whether there is a difference in ADHD diagnosis between patients who suffered penetrating foreign body injuries in a work accident and healthy volunteers who have not had a work accident before. We hypothesized that ADHD symptoms would be more dominant in individuals who suffered penetrating foreign body injuries after a work accident.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 257-2023, date: 27.12.2023) and conducted in accordance with the ethical standards. Written informed consent was obtained from all participants before enrollment. The authors declare that they have no conflict of interest and received no financial support for this research.

Study Design

This study was designed as a retrospective, controlled, comparative study. Forty-seven patients, who were admitted to the emergency orthopedics clinic with penetrating foreign body injuries and were operated on between January 2023 and December 2023, and forty-eight actively working control group patients, without previous penetrating foreign body injuries, were included in the study. Patients who were unable to communicate verbally, had a history of moderate to severe cognitive impairment, had alcohol and/or sedative-hypnotic addiction, had a psychiatric diagnosis, had mental retardation, and were using psychotropic medications were excluded from the study. The patients' age, gender, whether a patient had any previous accidents and whether these previous accidents required surgical treatment, years of work experience, work hours per week, amount of work hours after 5 pm, past medical history, use of tobacco products, amount of sleep (hours), if a family member with an ADHD diagnosis, and part of the body injured by a penetrating foreign body were recorded (Figure 1).

Adult ADHD Self-report Scale Version 1.1 Test

Adult ADHD self-report scale version 1.1 (ASRS-v1.1) is a self-rating scale used to assess symptoms of ADHD in adults within the scope of DSM-4 criteria (14). This scale consists of two parts: Part A (6 questions) and Part B (12 questions). For each item, participants are asked to indicate how often the specified symptom has occurred in the past six months. Answers are scored from 0 to 4; a score of 0 is given for never, 1 for rarely, 2 for sometimes, 3 for often, and 4 for very often. For all 18 items, responses of "often" or "very often" are considered positive, as indicated by shaded boxes on the questionnaire (14). If a patient endorses 4 or more of the Part A questions on the ASRS-v1.1 at these threshold levels, then the patient is considered positive. Although Part B is not used for diagnostic purposes, these items provide information

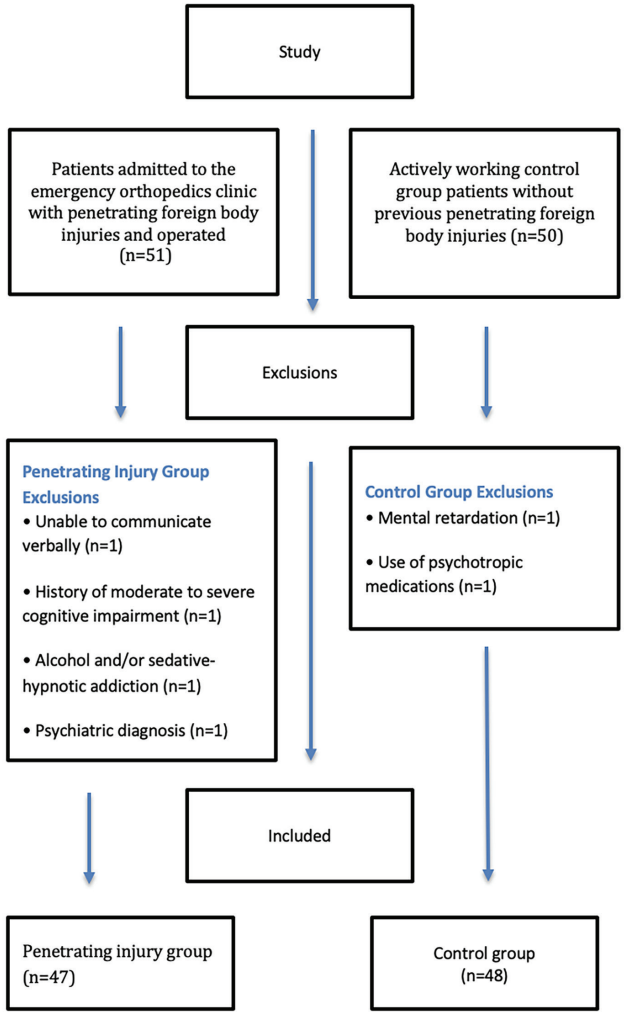

Figure 1. Flowchart of included and excluded patients

about the frequency of symptoms and may be helpful in determining what other symptoms the patient may be suffering from (14). The scale was adapted into Turkish by Doğan et al. (15). Since the ASRS-v1.1 scale is used in different ways in the literature, the scale is used both in scoring and with cut-off values (16,17). The ASRS-v1.1 test was administered by a psychiatrist who is an expert in the field.

Statistical Analysis

The relationship between the categorical information obtained in the study and the experimental and control groups was examined with the SPSS 20.0 software. The Kolmogorov-Smirnov test was used to examine whether the data of quantitative variables conformed to normal distribution. Whether the quantitative data differ significantly between groups is determined using a t-test for independent groups on data that conform to a normal distribution. Data that did not comply with the normal distribution were examined with the Mann-Whitney U test. Analysis among categorical variables was performed with a chi-square test. The statistical significance level was determined as $p<0.05$.

Results

The study included 95 patients, comprising 42 females and 53 males, with an average age of 35.1±11.5. In contrast, the control group had an average age of 38.4±13.5. Among these, 47 patients experienced work accidents, and the control group comprised 48 healthy individuals without work accidents. Demographic and social characteristics were comparable between the two groups (Table 1). No statistically significant difference in ASRS-v1.1 positivity was observed between the patient and control groups (p=0.093). The only notable distinction in working conditions was longer working hours after 5 pm in the group with work accidents (p=0.034).

Table 1. Comparison of demographic and social characteristics of individuals in the patient and control groups

		Patient	Control	p-value
Age		35.1±11.5	38.4±13.5	0.206 (2)
Gender	Female	17 (36.2%)	25 (52.1%)	0.088 (1)
	Male	30 (63.8%)	23 (47.9%)	
Individuals with ADHD diagnosis in the family	No	45 (95.7%)	45 (93.8%)	0.510 (1)
	Yes	2 (4.3%)	3 (6.3%)	
ASRS-v1.1 Part A+*		8 (17.0%)	3 (6.3%)	0.093
Smoking	No	22 (46.8%)	25 (52.1%)	0.379 (1)
	Yes	25 (53.2%)	23 (47.9%)	
Sleep duration (hours)		6.9±1.2	7.1±0.8	0.215 (2)
Weekly working hours		37.3±27.8	39.7±22.6	0.635 (2)
Working hours after 5 pm		1.8±2	1±1.4	0.034 (2)
Duration of employment (years)		8.2±8.7	10.3±14	0.383 (2)
Insurance status	No	25 (53.2%)	21 (43.8%)	0.237 (1)
	Yes	22 (46.8%)	27 (56.3%)	
Comorbidities	No	31 (66%)	37 (77.1%)	0.679 (1)
	HT	4 (8.5%)	4 (8.3%)	
	DM	3 (6.4%)	2 (4.2%)	
	Thyroid hormone disorder	1 (2.1%)	1 (2.1%)	
	Cardiac disease	1 (2.1%)	0 (0%)	
	Lung disease	2 (4.3%)	2 (4.2%)	
	Rheumatic disease	0 (0%)	1 (2.1%)	
	Epilepsy	2 (4.3%)	0 (0%)	
	Multiple diseases	3 (6.4%)	1 (2.1%)	

(1): Chi-square test, (2): Independent samples t-test
HT: Hypertension, DM: Diabetes mellitus, ADHD: Attention deficit and hyperactivity disorder, ASRS-v1.1: Adult ADHD self-report scale version 1.1
*Less than four shaded boxes were selected in ASRS-v1.1 Part A

In the patient group that experienced work accidents, a comparison between individuals with a notable ASRS-v1.1 Part A score (≥4) and those without a significant score (<4) revealed no discernible difference in various accident-related aspects. This includes factors such as how the accident occurred, the location of the foreign object entry, and the history of previous accidents, as detailed in Table 2.

We evaluated the scores of patient and control groups in three different scoring systems. When analyzing attention deficit subtype scores, hyperactivity/impulsivity scores, and ASRS-v1.1 total scores, it was statistically significant that there were higher scores in all three scoring systems, in the patient group compared to the control group (Table 3).

Discussion

Attention deficit hyperactivity disorder stands out as a crucial factor influencing accidents, injuries, and associated treatment costs. Characterized by attention deficit, hyperactivity, and impulsivity, ADHD has traditionally been a focus in pediatric studies. However, recent research emphasizes its role in adult accidents and unintentional injuries (18,19). This study specifically investigates cases where ADHD, identified through the ASRS V1-1 scale, intersects with workplace accidents involving foreign object penetration. Statistical analyses reveal noteworthy disparities in ADHD symptom severity between the accident-involved and non-accident groups. Total ASRS-v1.1 scores, attention deficit subtype scores, and hyperactivity-impulsivity subtype scores all exhibit statistically significant differences.

The association between ADHD and various health risks has been extensively explored in numerous studies. Chien et al.'s (20) study highlights a heightened total injury risk in individuals with ADHD. In another study, Ahn et al. (21) have shown that adults with ADHD are at increased risk of sustaining various types of injuries. Hailer et al. (22) observed a correlation between Legg-Calvé-Perthes patients and hyperactive behavior, coupled with increased physical activity during childhood. Ettinger et al. (23) reported an elevated frequency of seizures in epilepsy patients with a positive ASRS test. Moreover, studies consistently underscore the link between ADHD and an increased risk of unintentional injuries and accidents (24). Scans in this domain offer valuable insights into accident prevention (19). Notably, investigations into the connection between prior trauma, injuries, and ADHD symptoms reveal a significant relationship (24,25). Similar to these studies, this study aimed to evaluate the

Table 2. Effects of different characteristics of injury to ASRS-v1.1 part A score in the patient group

		ASRS-v1.1 negative patients in patient group*	ASRS-v1.1 positives in patient group**	p-value
Part of the body injured by a foreign object	Hand/Fingers	24 (61.5%)	7 (87.5%)	0.358
	Feet/Toes	13 (33.3%)	1 (12.5%)	
	Other lower extremity	2 (5.1%)	0 (0%)	
Whether there been any previous accidents	No	31 (79.5%)	4 (50%)	0.101
	Yes	8 (20.5%)	4 (50%)	
Whether previous accidents required surgery	No	36 (92.3%)	7 (87.5%)	0.539
	Yes	3 (7.7%)	1 (12.5%)	

Chi-square test
ASRS-v1.1: Adult ADHD self-report scale version 1.1
*Less than four shaded boxes were selected in ASRS-v1.1 Part A
**Four or more shaded boxes were selected in ASRS-v1.1 Part A

Table 3. Comparison of the patient and control groups in total ASRS-v1.1 scores, attention deficit subtype scores, hyperactivity/ impulsivity subtype scores

	Patient group	Control group	Z	p-value
	Mean±SD/Median	Mean±SD/Median		
Attention deficit subtype	11.60±5.53/10.00	8.90±4.21/8.50	-2.314	0.021*
Hyperactivity/impulsivity subtype	11.89±6.85/11.00	9.10±4.40/9.00	-2.034	0.042*
ASRS V.1.1 total score	23.30±11.30/20.00	17.98±6.39/18.00	-2.013	0.044*

Comparison of sub-type and total ASRS-v1.1 scores by Mann-Whitney U test
ASRS-v1.1: Adult ADHD self-report scale version 1.1
*Mann-Whitney U test

relationship between penetrating foreign body injury and ADHD and revealed that ADHD is associated with foreign body injury.

Baran Tatar et al. (26) utilized the ASRS-v1.1 for ADHD diagnosis, considering a positive ADHD subtype in individuals scoring over 24 points in 8 questions. In line with this approach, this study assessed the ASRS-v1.1 test, categorizing individuals into ADHD subtypes. Notably, 17% of the injured group tested positive for ADHD in Part A, compared to 6.3% in the control group. While the difference in ADHD-positive evaluations was not statistically significant, there was a proportionally higher incidence of ADHD in the accident group. Additionally, the injury group exhibited significantly higher scores on both hyperactivity-impulsivity and attention deficit subscales of ASRS, aligning with existing literature (18,27-29).

Adler et al. (30) highlighted that ASRS-v1.1 test results might be influenced by demographic factors such as age, gender, and race, indicating potential variations in ADHD diagnosis frequency. Consequently, comparing ADHD diagnosis frequency in specific patient groups with the general population may not yield accurate results. To address this, the study compared ASRS-v1.1 test results between the patient group with penetrating foreign body injury and a control group matched for age, gender, race, and occupation. The general population's ADHD prevalence is known to be 4.4%, yet in this study, ADHD diagnosis occurred in 17% of the patient group and 6.3% of the control group (27). The higher prevalence in the control group underscores the critical role of a well-matched control group in the study.

The study found no disparity in age and gender ratios between the injured and non-injured groups. Previous research indicates a "U"-shaped distribution of accidents and injuries across age groups, irrespective of ADHD presence (19,31). It's suggested that young men might experience more accidents and injuries than young women, which might emphasize the role of inexperience and high-risk behaviors (19,31). Adler et al. (30) noted the impact of demographic factors on ASRS-v1.1 test results, indicating potential variations in ADHD diagnosis frequency. Thus, comparing ADHD diagnosis frequency with the general population may not yield accurate results for specific patient groups. To address this, the study compared ASRS-v1.1 test results between the patient group with penetrating foreign body injuries and a well-matched control group in terms of age, gender, race, and occupation. In the general population, ADHD prevalence is reported as 4.4% or 5% (31,32). In this study, ADHD diagnosis occurred in 17% of the patient group and 6.3% of the control group, highlighting the crucial role of an adequately matched control group in interpreting study findings.

Study Limitations

While this study provides valuable insights, it is important to acknowledge its limitations. Firstly, the study is single-centered, potentially limiting the generalizability of findings to broader populations. The lack of inquiry into the duration of individuals' job tenure and the absence of specific questions about the duration of performing the same tasks could be considered a limitation, as experience levels might influence the likelihood of injury. Additionally, the categorization of injuries as work-related accidents, without a detailed exploration of psychosocial stressors, may overlook crucial factors influencing ADHD symptoms. The potential for a more defensive response in individuals perceiving their injuries as work-related accidents might introduce bias when completing the self-report scale. Despite these limitations, the study has several strengths. Firstly, it is one of the few controlled investigations focusing on the association between ADHD symptoms and penetrating foreign body injuries in occupational settings. Secondly, ADHD assessment was conducted using a standardized and widely accepted tool (ASRS-v1.1), administered by a specialist psychiatrist, which increases diagnostic accuracy and minimizes measurement bias. Moreover, the study addresses a relatively underexplored area, contributing valuable data to both orthopedic trauma and occupational mental health literature. Further investigations incorporating a more nuanced evaluation of psychosocial factors are warranted to enhance our understanding of the interplay between ADHD and occupational injuries.

Conclusion

This study establishes a significant association between penetrating foreign body injuries and ADHD. The findings suggest that implementing pre-employment ADHD assessments, specifically utilizing the ASRS-v1.1, could serve as a preventive measure in occupational settings prone to such injuries. We recommend the adoption of these assessments, particularly in industries involving manual work with sharp objects, where sustained attention is crucial.

Conclusions for Practice

- Attention deficit hyperactivity disorder symptoms may have an impact on the risk of occupational accidents, especially in occupations that require a high level of attention and involve handling sharp objects.

- The patients with foreign body penetration injuries had statistically significantly higher scores than the control group in all three scoring systems.

- Fatigue and working conditions, especially working hours after 5 pm, increase the likelihood of such accidents, especially in people with ADHD.

- Implementation of ADHD screening, particularly using the ASRS-v1.1, could be useful as a preventive measure in work environments where such injuries are common.

Ethics

Ethics Committee Approval: This study was approved by the the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 257-2023, date: 27.12.2023).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., A.I., M.Y., Concept: A.E., A.I., Design: M.A., M.B.G., S.S., M.Y., Data Collection or Processing: A.I., S.S., Analysis or Interpretation: M.A., M.B.G., M.Y., Literature Search: M.B.G., S.S., Writing: M.A., A.I.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Comparative Efficacy of Pericapsular Nerve Group and Suprainguinal Fascia Iliaca Blocks in Elderly Patients Undergoing Surgery for Subtrochanteric Femur Fractures: A Double-blind Randomized Controlled Trial

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Abstract

Aim: Peripheral nerve blocks (PNBs) are crucial for reducing opioid use and ensuring pain relief in elderly patients following hip fractures. Our study aimed to compare two recently recommended hip blocks regarding their effectiveness in postoperative analgesia.

Methods: This randomized, double-blind study primarily evaluated pain scores [numeric rating scale (NRS); at the 0th, 4th, 8th, 12th, and 24th hours] and total analgesic consumption in elderly patients scheduled for proximal femoral nailing between January 2022 and June 2024. The study involved three groups (n=25): control, pericapsular nerve group block (PENG), and suprainguinal fascia iliaca block (SIFIB) groups, all receiving the same anesthetic management and rescue analgesia plan.

Results: The NRS values of the control group were significantly higher than those of Group SIFIB at all hours except the postoperative 8th hour; the value was still higher than that of Group SIFIB (p=0.055). There was no significant difference between the control and PENG groups after the eighth hour postoperatively. The NRS values of the SIFIB group were significantly lower than those of the PENG group at all hours except for the 8th hour postoperatively. Group SIFIB required significantly lower analgesia than Group PENG (p<0.001).

Conclusion: This study indicated that SIFIB may be the preferred PNB for elderly patients with femur fractures, providing effective analgesia while minimizing analgesic consumption during the first 24 hours postoperatively.

Keywords: Frail elderly, hip fractures, peripheral nerves, suprainguinal fascia iliaca block, pericapsular nerve group block, pain

Introduction

Hip fractures pose a significant global issue, leading to increased morbidity and mortality, particularly among the elderly population (1). Regional anesthesia is the preferred method for improving patient safety after hip fracture surgery, especially in elderly patients (2). Effective pain management with minimal opioid use is an essential goal for elderly patients with femur fractures (3). Other than the well-known side effects of opioids for the general population, elderly patients are more prone to respiratory depression, hemodynamic instability, and increased side effects due to reduced metabolism of opioids (4). Additionally, the tendency to avoid these effects, leading to ineffective postoperative pain management, may increase the risk of delirium and cognitive dysfunction in the elderly population (5). Since there are preexisting high clinical frailty scores of these patients, immobility-related complications such as tendency towards venous

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thromboembolism, pulmonary aspirations, altered mental conditions, and cognitive impairment require more attention for early mobilization, if possible (6,7). Moreover, multimodal analgesia may not be an option to achieve these goals because non-steroidal anti-inflammatory drugs or even paracetamol may be contraindicated in this elderly group due to multiple comorbidities and possible drug interactions resulting from polypharmacy (8). With all this reasoning and these targets for elderly femur fracture patients, peripheral nerve blocks (PNBs) have been the analgesic plan of choice. However, a gold standard protocol for a block procedure has not been approved.

Lately, pericapsular nerve group block (PENG) targeting nociception of the anterior hip capsule and fascia iliaca blocks (FIBs), preferably the suprainguinal FIB (SIFIB), has been in the spotlight of research to determine and compare the analgesic efficacy and motor impairment after these blocks (9,10). Therefore, we designed a prospective study to identify a PNB suitable for elderly femur fractures, resulting in sufficient analgesia with minimum analgesic consumption and preserving motor function. We also focused on block procedures, specifically examining the duration required to perform the block. We searched for the tertiary effects on outcomes such as postoperative serious events and intensive care unit (ICU) admission.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was obtained from University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinicial Research Ethics Committee (approval no.: 18-2021, date: 24.11.2021). The study was recorded at clinicaltrials.gov (NCT06277648, 02/19/2024).

Study Design and Population

We designed a double-blind, randomized, controlled study and assessed patients with subtrochanteric femur fractures scheduled for proximal femoral nailing (PFN) after January 2022 for eligibility. We conducted the study in our tertiary care hospital until June 2024, in accordance with the principles outlined in the Helsinki Declaration. After obtaining written informed consent, 75 patients (3 groups; 1:1:1 distribution; n=25) were allocated, and the Consolidated Standards of Reporting Trials flow diagram was used to present the progression (Figure 1). Patients eligible for inclusion in this study were those over 65 who had undergone PFN and had an American Society of Anesthesiologists (ASA) Physical Status classification of I to IV. These patients and their relatives were provided with information about the PNBs included in the study. They were educated on evaluating pain scores [numeric rating scale (NRS)]. Patients were excluded if they had one of the following criteria: refusal to participate, a history of neurological deficits or neuropathy, infection at the site of block application, coagulopathy, or allergy to local anesthetics. Patients were also excluded if they had cachexia, an actual body weight of less than 45 kilograms, severe cardiopulmonary insufficiency, renal impairment, or mental illness. The patients were excluded if there was a change of surgical plan or if the surgery was prolonged due to orthopedic complications of more than 3 hours, necessitating conversion of spinal anesthesia to general anesthesia.

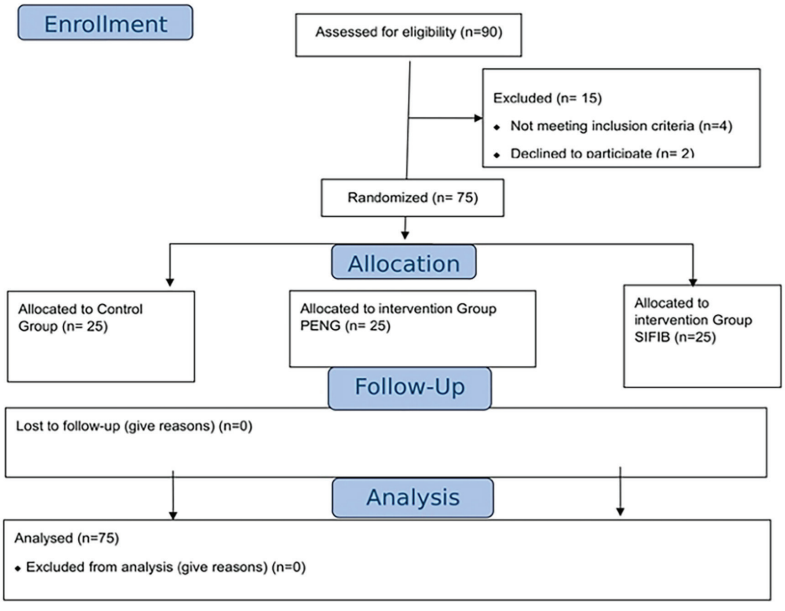

Figure 1. Consort flow diagram
PENG: Pericapsular nerve group block

Randomization, Blindness, and Standardization

Randomization was designed for 3 groups (n=25 for each group), named Groups A, B, and C, in a 1:1:1 ratio, using a computer-based algorithm and sealed in opaque envelopes by the surgeon assigned to the study. The investigator anesthesiologist selected an envelope based on the number written on it and proceeded with PENG if it was Group A and SIFIB if it was Group B. If the patient was in Group C, there was no intervention other than intravenous (IV) analgesia. The orthopedic surgeon responsible for the study was blinded to the study groups. This surgeon was the sole evaluator of postoperative pain scores, total analgesic consumption, and motor block. All block procedures were performed by the primary investigator (B.C.). The duration of block performance and number of needle manipulations before local anesthetic injections were recorded by the anesthesia technician assisting the procedure.

All patients received standard spinal anesthesia procedures with 10 mg of heavy Marcaine (2 mL of bupivacaine 0.5%) and 25 µg of fentanyl (0.5 mL) at the L3-4 intervertebral space with the aid of midazolam 0.02 mg/kg and ketamine 0.3 mg/kg for analgesia to achieve a sitting position. Patients in the study groups (Group PENG and SIFIB) received block procedures consisting of 30 mL of 0.375% bupivacaine postoperatively in the recovery room under monitoring. The same multimodal analgesia plan was ordered for all participants, consisting of paracetamol 1 g (four times daily), tenoxicam 20 mg (daily), and dexamethasone 8 mg once postoperatively, as our routine clinical practice. They received rescue analgesia only if they had persistent pain scores higher than 4 out of 10 or asked for analgesia, with tramadol administered at 1 mg/kg (maximum daily dose: four times daily).

Interventions: Block Procedures

The primary investigator (B.C.) performed a PENG block with the patient in a supine position following proper skin disinfection. Under the guidance of a low-frequency curvilinear ultrasound probe, the iliopubic eminence and the psoas tendon were identified by sliding the probe cephalad from the inguinal crease. Following negative aspiration, local anesthetic was injected between the periosteum and psoas tendon (Figure 2).

For SIFIB, the high-frequency linear probe was placed medial to the anterosuperior iliac spine in a parasagittal orientation to visualize the bow tie appearance formed by the sartorius, internal oblique, and iliacus muscles. The needle tip was placed under fascia iliaca through an in-plane approach, and local anesthetic was injected from the caudad to the cephalad direction (Figure 3).

Outcome Measures

The primary outcome of this study is the pain score. They were assessed by the same orthopedic surgeon using the NRS (NRS, which ranges from 0 to 10, where zero represents the absence of pain, and 10 signifies the worst imaginable pain) at postoperative intervals of 12, and 24 hours.

Secondarily, the blinded orthopedic surgeon recorded the number of times rescue analgesia was applied within 24 hours postoperatively. Block performances were also compared based on the duration of interventions and by assessing the presence of motor block, specifically hip adduction, at the postoperative 6th hour. The incidence of postoperative serious events and ICU admissions was also noted.

Sample Size

The sample size was based on detecting a change of 2 units or more in mean pain scores (the primary outcome)

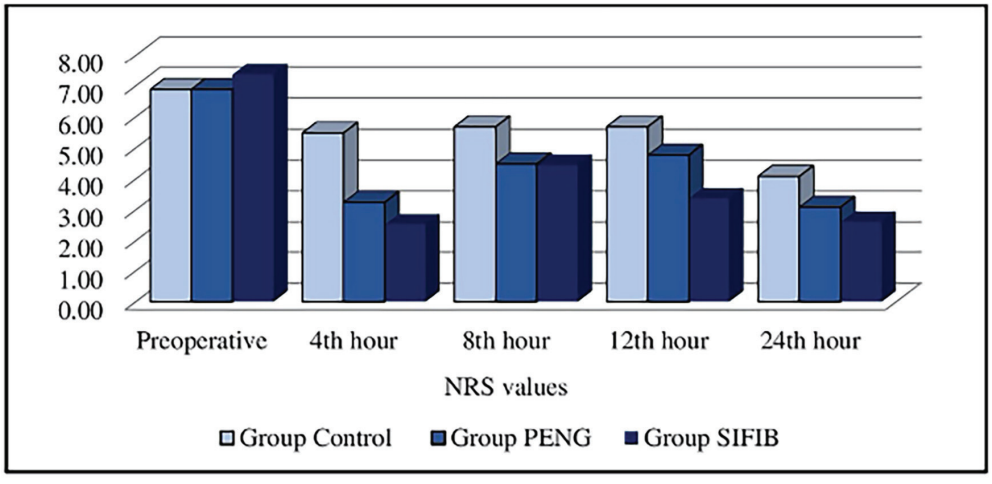

Figure 2. PENG block
NRS: Numeric rating scale, PENG: Pericapsular nerve group block, SIFIB: Suprainguinal fascia iliaca block

using analysis of covariance on the outcomes at the follow-up time point. Using an estimated standard deviation of 2 units for pain scores (0-10) with standard type I and type II error rates, we calculated that 20 patients per group would be needed. To allow dropouts or exclusions, we enrolled 25 patients in each group to have a total sample size of 75 participants.

Statistical Analysis

The SPSS 27.0 program was used in the analyses. Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov-Smirnov test. Analysis of variance (Tukey test) was used to analyze quantitative independent data with normal distribution. The Kruskal-Wallis and Mann-Whitney U tests were used to analyze quantitative independent data with non-normal distribution. The chi-square test was used in the analysis of qualitative independent data. The statistical significance threshold was $p<0.05$.

Results

There were no significant differences between the groups in terms of demographic data, ASA scores, and the Charlson Comorbidity Index (CCI) (Table 1).

In terms of NRS values, there were no significant differences between block groups in preoperative values (Figure 4). The NRS values of the control group were significantly higher than Group SIFIB at all hours except the postoperative 8th hour ($p=0.00$) (Figure 2). There was also no significant difference between the control group and the PENG group after the eighth hour postoperatively (Figure 4). Accordingly, the NRS values of the SIFIB group were significantly lower than those of the PENG group at all hours except the postoperative 8^{th} hour. The value was still lower than PENG ($p4^{th}=0.000$, $p8^{th}=0.055$, $p12^{th}=0.000$, $p24^{th}=0.002$) (Figure 4).

Moreover, the total analgesia requirements within 24 hours were significantly higher in the control group ($p<0.001$) (Figure 5). Group SIFIB required significantly lower analgesia than Group PENG ($p<0.001$) (Figure 5).

The rate of motor blockade after 6 hours did not differ significantly between groups ($p=0.684$) (Table 1). Moreover, the incidence of postoperative serious events and ICU admissions was not significantly different between groups (Table 1). However, the duration of block performance was significantly longer in Group PENG than in Group SIFIB ($p=0.001$) (Table 1).

Discussion

Our study revealed that the elderly patients receiving SIFIB had better analgesia with minimum analgesic consumption at postoperative 24 hours when compared not only with the control group but also with the patients receiving PENG block and preserving motor function. This study also presented the duration of maximum efficacy for each fascial plane block, typically lasting 8 hours. However, between the two, SIFIB proved to have prolonged efficacy, still high enough to outperform the control group until 24 hours postoperatively. Additionally, the shorter duration of SIFIB performance compared to the PENG block underlines the practicality of this block, especially for unstable patients with a high comorbidity index or under anticoagulation.

Anesthesia and analgesia management in femur and hip surgeries is an ongoing area of research, since no standalone protocol has proved efficient for all surgical techniques in this anatomical area with its multi-neural source of postoperative pain (11). Besides, the older population has been a particular concern due to their existing fragility and comorbidities, making pain

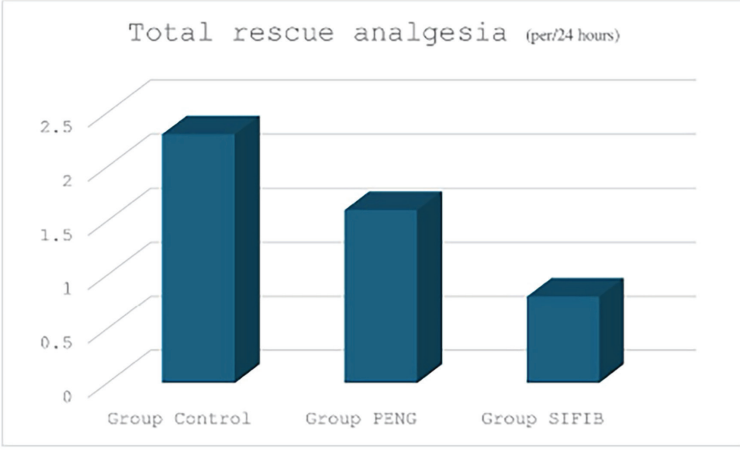

Figure 3. Supra-inguinal ascia iliaca block
PENG: Pericapsular nerve group block, SIFIB: Suprainguinal fascia iliaca block

management an essential determinant of mortality and morbidity (3). The challenge is ensuring adequate pain management and avoiding the side effects of the possible multimodal analgesia protocols (5,6). Accordingly, these elderly populations generally have CCI over four and ASA scores of III and IV, as observed in our study population. These features make a method that is both effective and simple superior for this patient group, especially for patients with unstable comorbidities or those using anticoagulation. Although most of the research on pain

Table 1. Demographics related to patients, nerve blocks and postoperative outcomes

			Group control[1]	Group PENG[2]	Group SIFIB[3]	p-value	
Age (year)	**Mean±SD**		79.0±9.8	78.2±9.2	80.0±6.7	0.784	A
	Median		77.0	80.0	81.0		
Gender	**Female**	**n-%**	16-64.0%	16-64.0%	14-56.0%	0.799	X^2
	Male	**n-%**	9-36.0%	9-36.0%	11-44.0%		
BMI	**Mean±SD**		25.7±6.0	26.0±6.8	25.2±5.7	0.906	A
	Median		24.3	26.3	24.8		
ASA score	**I**	**n-%**	1-4.0%	6-24.0%	4-16.0%	0.115	X^2
	II	**n-%**	21-84.0%	10-40.0%	15-60.0%		
	III	**n-%**	3-12.0%	8-32.0%	6-24.0%		
	IV	**n-%**	0-0.0%	1-4.0%	0-0.0%		
CCI	**Mean±SD**		4.4±1.4	4.5±1.6	4.8±1.1	0.423	K
	Median		4.0	4.0	5.0		
Duration of block performance (min)	**Mean±SD**			5.2±1.2	4.1±1.1	**0.001**	K
	Median			5.0	4.0		
Motor block	**(No)**	**n-%**	0.0%	22-88.0%	21-84.0%	0.684	X^2
	(Yes)	**n-%**	0.0%	3-12.0%	4-16.0%		
Postoperative ICU	**(No)**	**n-%**	18-81.8%	24-96.0%	20-83.3%	0.266	X^2
	(Yes)	**n-%**	4-18.2%	1-4.0%	4-16.7%		
Postoperative serious event	**(No)**	**n-%**	17-77.3%	22-88.0%	18-75.0%	0.475	X^2
	(Yes)	**n-%**	5-22.7%	3-12.0%	6-25.0%		

A: ANOVA, K: Kruskal-Wallis (Mann-Whitney U test), X^2: Chi-square test, [1]Difference between Group control $p<0.05$, [2]Difference between Group SIFIB $p<0.05$
SD: Standard deviation, PENG: Pericapsular nerve group block, SIFIB: Suprainguinal fascia iliaca block, BMI: Body mass index, ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity Index, ICU: Intensive care unit

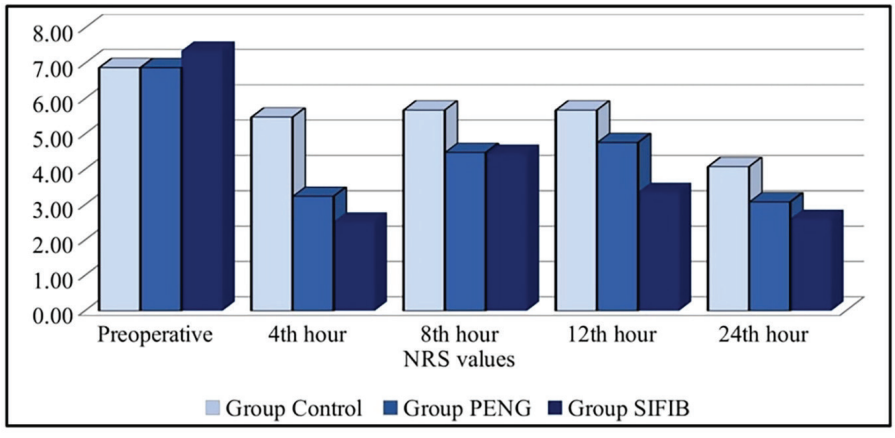

Figure 4. Comparison of NRS values
PENG: Pericapsular nerve group block, SIFIB: Suprainguinal fascia iliaca block, NRS: Numeric rating scale

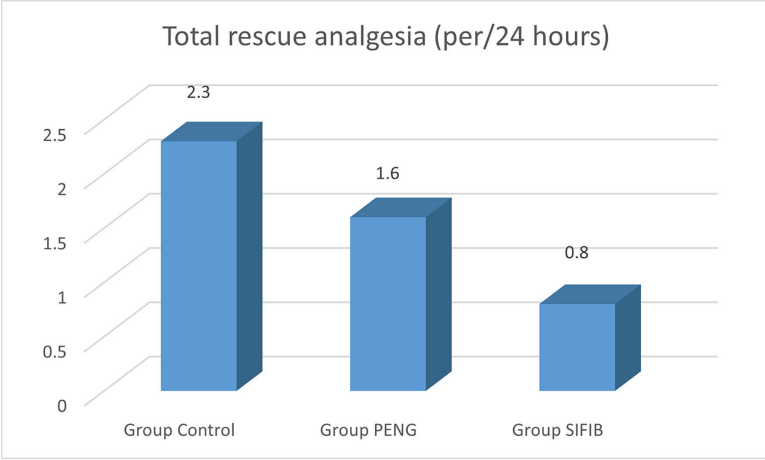

Figure 5. Comparison of total rescue analgesia
PENG: Pericapsular nerve group block, SIFIB: Suprainguinal fascia iliaca block

management focuses on hip prostheses, the orthopedic approach to these fragile patients mostly involves femur surgeries to decrease surgery-related postoperative complications (12). That is why the search for analgesia management for elderly femur fractures, which involve the same anatomical concerns as areas innervated by the femoral, lateral femoral cutaneous (LFCN), and obturator nerves, is guided by these protocols, of which we selected PENG and SIFIB from among this limited range (13,14).

Recent studies have shown that compared to IV analgesic treatment or sham block, PENG block provides adequate analgesia for elderly patients after neck and intertrochanteric femur fractures (15,16). Moreover, Li et al. (17) demonstrated its additional advantage in aiding the positioning of spinal anesthesia along with its long-lasting analgesic effectiveness for 24 hours postoperatively, possibly achieved by adding dexamethasone to the local anesthetic solution. The ease of spinal positioning was compared between femoral block, SIFIB, and PENG. Suprainguinal fascia iliaca block and PENG were found to be more effective (18,19). That success is predictable, as Girón-Arango et al. (20) described the PENG block targeting the femoral nerve, obturator nerve, and accessory obturator nerve in 2018. However, as in our study, a small amount of ketamine (IV) could be sufficient to aid in achieving spinal anesthesia in patients with subtrochanteric femur fractures. PNBs could be applied postoperatively just before the diminishing effect of existing analgesia with neuraxial anesthesia. Besides, the target of PNBs could be a disadvantage if the surgical area comprises LFCN innervation, the PFN surgery, mostly preferred in elderly subtrochanteric femur fractures as described in this study. The reason why the PENG block was not as successful in our study as it is in the literature may be that the surgical approach in these fractures falls more within the innervation field of the LFCN. The location of the incision and the type of surgical approach used in hip surgery can influence the source of postoperative pain. Therefore, PNBs should be tailored to match the specific needs of each patient, particularly in the elderly population, which is the focus of this study. Although PENG has become widespread as a prominent block in hip fractures, the possible disadvantage of PENG has driven the motivation for studies like ours to compare it with FIB, and our findings still favor PENG for providing better analgesia (21,22). However, SIFIB has gained interest over FIB for lower extremity surgeries targeting LFCN, resembling the effect of a lumbar plexus block (23). Our focus is on the potential of SIFIB as a rival to the PENG block, a topic shared by recent studies involving hip arthroplasty, which have shown conflicting results (24,25). While Vamshi et al. (24) found superior analgesia with PENG over SIFIB and presented a lower incidence of quadriceps weakness by observing knee extension and hip adduction, Keskes et al. (25) exhibited adequate but similar pain scores at all hours during the first 24 hours postoperatively. Our results show that PENG ensures analgesia for only eight hours postoperatively, while SIFIB provides it for 24 hours except at the 8th hour, which is the expected duration of the highest effectiveness for a fascial plane block. Interestingly, this occurred in both the PENG and SIFIB groups. This phenomenon could be due to rebound pain, and the lasting effect of SIFIB, along with rescue analgesia, could be sufficient in the following hours. Nevertheless, the required total analgesic requirement within 24 hours was lower in the SIFIB group. Although the studies comparing these two blocks have found higher analgesic consumption in the SIFIB, the study populations consisted of patients undergoing hip arthroplasties. Few studies have examined SIFIB in hip fractures as in our study.

Nuthep et al. (26) observed the superiority of the SIFIB and PENG combination in elderly patients undergoing hip fracture surgery. Pain scores were similar within 48 hours postoperatively (26). That observation could support our results that SIFIB may be superior to PENG in analgesic management, not in hip arthroplasty, but rather in femur fracture surgeries that cover the LFCN area associated with pain stimuli. Future studies could further investigate this hypothesis by adding an LFCN block to PENG in hip fractures to compare the analgesic efficacy with SIFIB, as PENG with an LFCN block has been shown to be more effective than SIFIB in hip arthroplasty (9).

Our study is the first prospective randomized study to compare SIFIB and PENG in elderly hip fracture surgeries by including a control group. Most of the previous literature did not have a control group to further evaluate the effectiveness of each intervention (27,28). Besides its significant results of perioperative pain scores and total analgesic consumption favoring SIFIB, we demonstrated a similar incidence of motor block, specifically for hip adduction. Although motor block is generally considered undesirable after a PNB, it should not be a deciding factor in selecting the type of block when postoperative mobilization is not feasible or necessary, as demonstrated by the patient group in our study. Thus, determining which PNB is more effective may yield more favorable results when the evaluation primarily focuses on its practical advantages, aside from analgesic efficacy. Based on this logic, we evaluated the practicality of PNB in our study groups. Notably, the duration of the block performance with SIFIB was lower than that of PENG, which is not surprising because of its superficial localization and ease of application. That property of SIFIB could be fundamental for elderly patients on anticoagulation, not only for analgesia but also for anesthesia, either as a sole technique or in combination with a sciatic block in lower extremity surgeries of high-risk patients (29).

Study Limitations

Our study had some limitations. We could not observe the dynamic NRS scores of the patients because there was no rehabilitation program after the surgery. Apart from this, we evaluated motor block only by hip adduction due to restricted knee extension post-surgery. Following this study's results, a question was raised to compare pain scores after SIFIB and PENG, preferably by adding LFCN, with a more extensive study population of elderly femur fractures to analyze the rebound pain within 24 hours.

Conclusion

In searching for a PNB for elderly femur fractures, our study compares the SIFIB and PENG block and finds SIFIB to be the preferable choice to ensure efficient analgesia with minimum analgesic consumption during the first 24 hours after surgery while also preserving motor function. In addition, the practicality of SIFIB performance as an easily visualized superficial block gains an advantage, especially for fragile elderly patients with comorbidities possibly needing anticoagulation and postoperative ICU admission. These elderly patients should still receive rapidly administered, long-lasting, safe analgesia management, as SIFIB was shown to be the best-suited candidate for this goal.

Ethics

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinicial Research Ethics Committee (approval no.: 18-2021, date: 24.11.2021).

Informed Consent: Verbal and written consent was received from all patients.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: B.C., S.D., O.S., Concept: B.C., Design: B.C., Data Collection or Processing: B.C., S.D., O.S., Analysis or Interpretation: B.C., Literature Search: B.C., Writing: B.C.

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Original Article

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Evaluation of Dentistry Faculty Preclinical Students' Approach to Ergonomics and Occupational Diseases in Dentistry

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Abstract

Aim: The prevalence of musculoskeletal disorders caused by non-ergonomic work practices in dentistry is notably high. Alarmingly, these symptoms can manifest even in students who have not yet begun clinical practice. This study aims to assess the ergonomic awareness and knowledge of occupational diseases among preclinical dental students and to raise awareness before they enter their professional careers.

Methods: The cross-sectional prospective survey study included 447 students who were in the preclinical period in 2023-2024. A structured questionnaire was administered, consisting of sections pertaining to demographic information, health status, habits, awareness, risk factors, and clinical symptoms.

Results: Evaluation of awareness factors revealed that 56.2% of participants demonstrated an awareness rate exceeding 50%. Furthermore, awareness levels increased significantly from the first to the third year of study ($p<0.001$). No statistically significant difference was observed for awareness and risk factors in terms of gender.

Conclusion: The findings indicate that preclinical dental students have insufficient awareness of ergonomic risks and occupational diseases. Integrating ergonomic knowledge into the early stages of dental education could enhance self-awareness, help prevent occupational disorders, and support the long-term ability of dentists to sustain their professional practice.

Keywords: Ergonomic, occupational diseases, dental students

Introduction

The increasing emphasis on the value of the individual has given rise to occupational ergonomics, a discipline focused on designing working and living environments that align with human characteristics. This discipline explores the interplay between individuals, their work, and their environment, culminating in the science of ergonomics (1). The application of ergonomic principles in the workplace fosters a harmonious relationship between individuals and their roles while safeguarding their physical and psychological well-being and ensuring occupational safety. Moreover, it addresses health concerns, mitigates workforce attrition, alleviates fatigue and stress, and minimizes the risk of occupational accidents and illnesses. Ergonomics holds particular significance in dentistry, a profession identified as potentially hazardous in the Occupational Safety and Health Administration (2). Dentists face numerous occupational hazards that contribute to work-related illnesses. These challenges include the stress inherent in a profession requiring high levels of concentration and precision, repetitive and physically demanding movements in confined spaces, prolonged use of high-precision tools that strain the musculoskeletal system, and sustained postures during procedures (3,4).

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While dentists prioritize the oral and dental health of their patients, they often neglect their own posture and ergonomic needs. It is recognized that musculoskeletal diseases are more prevalent among dentists in comparison to the general population (5). Incorporating ergonomic principles in dentistry empowers dental practitioners and their teams to perform their duties without compromising their physical health, thereby improving patient outcomes. The primary objective of ergonomics in dentistry is to preserve musculoskeletal health and promote mental well-being by reducing stress and fatigue. This is achieved through the optimization of equipment design and the working environment for dental professionals (1). A fundamental aspect of dental ergonomics is maintaining appropriate working postures during procedures. Musculoskeletal disorders represent the most prevalent category of occupational injuries arising from the disregard of ergonomic principles. These disorders are notably common among dentists and contribute significantly to early retirement decisions (6). Importantly, these conditions are also observed among dental students in training (7). The early onset of symptoms in students who have yet to encounter the rigors of clinical practice underscores the importance of raising awareness about ergonomic work practices.

In this study, we hypothesized that ergonomic awareness and understanding of occupational diseases are inadequate among preclinical dental students. In light of these considerations, the primary objective of this study is to raise awareness among preclinical dental students, while the secondary aim is to provide guidance to educational programs. By providing dental students with knowledge of potential risks and effective coping strategies, they can raise awareness and reduce the likelihood of developing occupational injuries, enabling them to pursue long and healthy careers.

Material and Methods

Compliance with Ethical Standards

Ethical approval for this structured survey study was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University (approval no.: 2024/04-02, date: 18.04.2024). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Design and Population

This survey was administered to preclinical students (1st, 2nd, and 3rd-year) at the Faculties of Dentistry at Lokman Hekim and Sivas Cumhuriyet Universities. Participation was voluntary and confidentiality was strictly maintained. Prior to the commencement of the survey, all participants were provided with comprehensive information about the study, and informed consent was obtained through a consent form.

The structured questionnaire, which was developed based on a review of the extant literature, consisted of the following sections:

1. Demographic information
2. Health status
3. Habits
4. Awareness
5. Risk factors
6. Clinical symptoms (Tables 1, 2).

The target population included students aged 20-35 years in the preclinical period. Exclusion criteria included pregnant individuals, those with a history of musculoskeletal surgery, and those with rheumatic, neuromuscular, or genetic muscle and bone disorders. Furthermore, participants who declined to participate in the study or provided unreliable answers (i.e., selecting the same option in all answers or providing inconsistent answers in questions measuring similar concepts) were excluded from the study (Figure 1).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 23.0 software (IBM Corp. Released 2012). IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). In the present study, the total population size was determined, and a minimum of 441 subjects should be included in the study when the sample size was calculated with a 95% confidence interval and a 3% margin of error (8). The analysis began by determining whether the dataset met the requisite assumptions, and non-parametric tests were employed due to the non-normal distribution of the data.

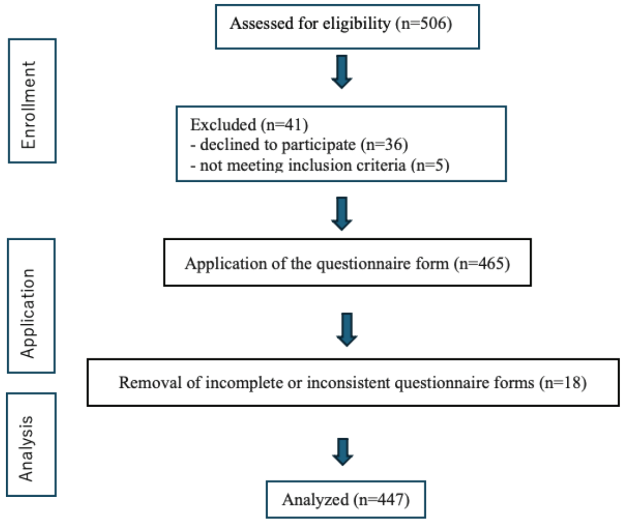

Figure 1. Flowchart of the study

- Normality test: The Kolmogorov-Smirnov test was employed to evaluate the normality of data distribution.
- Categorical data analysis: Cross-evaluations of categorical data were conducted using the chi-square test.
- Awareness and risk scales by class and body mass index (BMI): General means were calculated using a Kruskal-Wallis test.
- Gender-based comparisons: The Mann-Whitney U test was used to compare the mean awareness rates and risk scales between male and female participants.
- Combined variable analysis: As the data were numerically transformed rather than categorical, a general linear model with analysis of covariance (ANCOVA) was used to assess the combined effects of the variables.

A p-value of <0.05 was considered the threshold for statistical significance in all tests.

Results

Scale Reliability Assessment

The general reliability score of the awareness scale was assessed using the Kuder-Richardson 20 (KR-20) reliability coefficient, which was calculated to be 0.767. Since this value exceeds the commonly accepted threshold of 0.7, the scale was deemed to be reliable. Similarly, the risk scale's reliability was evaluated using Cronbach's alpha coefficient, which was determined to be 0.825. This value indicates that the scale is reliable in its current form and that its items are consistent with the overarching structure.

Results on Demographic Information, Health Status, and Habits

The study included 447 students, with a mean age of 20.47±1.85 years. Among the participants, 62.2% (n=278) were female, and 37.8% (n=169) were male. Based on the BMI classification system, the majority (70.7%) were categorized as having a normal body weight. Most participants (96%) reported no chronic illnesses, and 88.1% did not take regular medication.

Regarding lifestyle habits, 63.8% of participants did not engage in regular exercise, while the majority did not smoke (74.7%) or consume alcohol (77.9%). Right-handedness was predominant, with 91.1% of respondents indicating they typically write with their right hand. Notably, 60.6% of participants reported not employing any stress management strategies. A majority (73.6%) believed that musculoskeletal disorders are the most common occupational diseases associated with non-ergonomic work in dentistry. A very low proportion of students (4%) thought that the wrist would be affected by non-ergonomic work. The results of the study indicated that 13.9% of respondents believed that symptoms of occupational illness manifested within the first five years of employment, while 38% indicated that this occurred within the subsequent six to ten years.

Results for the Awareness Section

The findings revealed that while the majority of students were familiar with the term "ergonomics" (69.4%), they lacked knowledge of its application in dentistry (61.1%). Over 50% of participants reported that they were unable to work according to a clockwise schedule (59.3%), despite being aware of the existence

Table 1. Demographic information, health status and habit sections

SECTION 1: DEMOGRAPHIC INFORMATION			
Age			
Gender	☐ Female		☐ Male
What grade are you in?	☐ 1	☐ 2	☐ 3
SECTION 2: HEALTH STATUS			
What is your height?			
What is your weight?			
Do you have a chronic illness?	☐ Yes		☐ No
Do you take any medication regularly?	☐ Yes		☐ No
Have you had any musculoskeletal surgery?	☐ Yes		☐ No
SECTION 3: HABITS			
Do you exercise regularly?	☐ Yes		☐ No
Do you smoke?	☐ Yes		☐ No
Do you drink alcohol?	☐ Yes		☐ No
Which hand do you use for writing?	☐ Right		☐ Left
Is there a method you use for stress management (breathing exercise, yoga, etc.)?	☐ Yes		☐ No

of occupational diseases (65.1%). A significant proportion (86.4%) demonstrated a lack of understanding regarding four-handed dentistry. Furthermore, 57% were unaware of specific occupational illnesses associated with their profession, and 71.8% exhibited limited knowledge about carpal tunnel syndrome.

Despite these gaps, 52.3% were aware of the correct working posture for clinical settings. Most participants (79.9%) acknowledged the role of ergonomics in occupational diseases and workplace accidents, while 85.5% agreed that ergonomics impacts work efficiency and performance. Additionally, 84.6% perceived a link between ergonomics and anthropometry. Overall, 56.2% of participants achieved an awareness rate exceeding 50% (n=251).

Statistical analysis revealed a significant increase in awareness rates from the first to third grade. The proportion of participants with a level of awareness of 50% or higher increased from first to third grade (36.2%, 47.3%, and 89.1%, respectively) (Pearson chi-square,

Table 2. Awareness, risk factors and clinical symptoms section

SECTION 4: AWARENESS					
Have you heard the term ergonomics before?	☐ Yes	☐ No			
Do you have any information about ergonomics in the dental profession?	☐ Yes	☐ No			
Do you know the working position according to the clock dial?	☐ Yes	☐ No			
Do you know the occupational diseases specific to the dentistry profession?	☐ Yes	☐ No			
Do you know about four-handed dentistry?	☐ Yes	☐ No			
Do you know about the most common musculoskeletal diseases in the dental profession?	☐ Yes	☐ No			
Do you know the correct working posture when you go to the clinic/patient care?	☐ Yes	☐ No			
Do you know what carpal tunnel syndrome is?	☐ Yes	☐ No			
Does ergonomics affect work accidents and occupational diseases?	☐ Yes	☐ No			
Does ergonomics affect work efficiency and performance?	☐ Yes	☐ No			
Are ergonomic conditions affected by the anthropometric characteristics of the individual? (Anthropometry: It is a science based on systematic techniques that dimension the physical properties of the human body with the principles of measurement).	☐ Yes	☐ No			
SECTION 5: RISK FACTORS					
	Strongly Disagree	**Disagree**	**No opinion**	**I agree**	**Strongly Agree**
The standing patient treatment position is ergonomic					
A high body mass index influences the occurrence of occupational discomfort.					
Regular exercise helps to prevent occupational discomfort that may occur due to work that is not suitable for ergonomics.					
Long working hours or insufficient rest periods are ergonomic risk factors.					
Noise and vibration of the tools used are ergonomic risk factors.					
Repetitive movements are ergonomic risk factors.					
Long-term use of unsuitable gloves is an ergonomic risk.					
Besides physical factors, psychosocial factors and personal characteristics are factors in occupational accidents.					
Sound insulation in the working environment is an ergonomic risk factor.					
SECTION 6: CLINIC SYMPTOMS					
What are the most common occupational disorders due to non-ergonomic work in dentistry?	☐ **Hearing disorders** ☐ **Vibration syndrome** ☐ **Musculoskeletal disorders** ☐ **Visual impairments**				
In which region does pain occur most frequently due to non-ergonomic work in dentistry?	☐ **Neck**	☐ **Waist**	☐ **Back**	☐ **Wrist**	
What is the percentage of dentists reporting at least one musculoskeletal disease symptom at some point in their lives?	☐ **25%**	☐ **55%**	☐ **85%**	☐ **98%**	
Occupational disease symptoms are reported more frequently in which years of working life?	☐ **1-5 years**	☐ **6-10 years**	☐ **7-15 years**	☐ **16-20 years**	

p<0.001). The mean awareness scores also increased significantly across grades (Kruskal-Wallis, p<0.001).

When analyzed by gender, 56.8% of females and 55.0% of males achieved awareness levels above 50%. This difference was not statistically significant (Pearson chi-square, p=0.709). Similarly, the mean awareness scores for females (54.77±24.57) and males (54.43±23.78) did not differ significantly (Mann-Whitney U test, p=0.721). BMI-related comparisons revealed no significant differences in awareness rates or mean scores across categories (Kruskal-Wallis, p>0.05) (Table 3).

Results for the Risk Factors Section

Regarding risk factors, 45.9% of students lacked knowledge about the ergonomic implications of outpatient care. Most participants (77.7%) identified elevated BMI as a risk factor for occupational diseases, and 79.6% recognized regular exercise as a preventive measure. A large proportion (84.5%) identified extended working hours and insufficient rest periods as ergonomic risk factors. Furthermore, 59.4% considered improper glove use to be a potential ergonomic hazard.

Psychosocial factors and personal characteristics were recognized as contributors to occupational diseases by 81.7% of participants. Additionally, 58.3% identified the sound and vibration of tools as ergonomic risks, and 47.7% viewed inadequate sound insulation as a hazard. Repetitive movements were cited as risk factors by 59.7% of students.

No statistically significant differences were found between the average risk scale scores by grade (Kruskal-Wallis, p=0.117) (Table 4). No statistically significant differences were observed in mean risk scores by gender, although females scored higher (3.81±0.52) than males (3.62±0.79) (Mann-Whitney, p=0.162). The results regarding the evaluation of the participants' risk scale general score averages according to BMI are not statistically significant (Kruskal-Wallis, p=0.224) (Table 3).

Using a General Linear Model-ANCOVA analysis, the combined effects of variables on the total mindfulness scale scores were statistically significant [F(21,419)=12,160, p<0.001]. Independent variables with marginal significance included grade, BMI, and alcohol use. Awareness scores increased significantly with academic grades. Higher levels of awareness were demonstrated by obese participants and those who consumed alcohol (Figure 2).

When adjusted for gender and grade, no significant differences in awareness scores were observed in the first grade. However, males in the second grade and females in the third grade demonstrated higher scores (Table 5). A positive correlation was identified between awareness and risk scores within the normal weight group (n=316, r=0.184, p=0.001).

Discussion

The human body is not anatomically designed to maintain a fixed position for prolonged periods. Resting periods allow for the repair of damaged tissues. However,

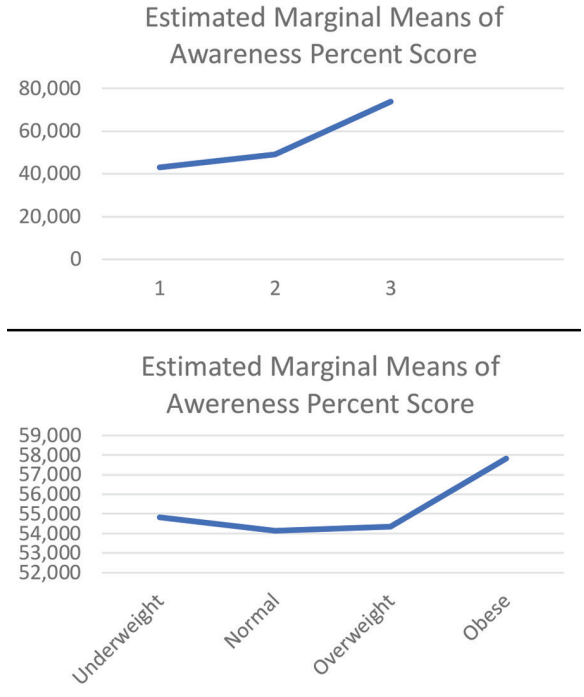

Figure 2. Line graph of corrected awareness total percentage scores according to grades (right) and line graph of corrected awareness total percentage scores according to BMI categories (left)
BMI: Body mass index

Table 3. Mean ± SD and median values of awareness and risk factors sections according to BMI categories

BMI category	N	Mean ± SD for awareness section	Median for awareness section	Mean ± SD deviation for risk factors section	Median for risk factors section
Underweight	40	52.50±25.17	**50.00**	**3.65±0.48**	**3.72**
Normal	316	54.60±24.42	**55.05**	**3.76±0.63**	**3.88**
Overweight	69	55.86±24.51	**54.54**	**3.65±0.80**	**3.81**
Obese	22	55.37±20.21	**53.24**	**3.82±0.43**	**3.83**
Total	447	54.64±24.25	**54.39**	**3.74±0.64**	**3.85**

SD: Standard deviation, BMI: Body mass index

Table 4. Mean ± SD and median values of awareness and risk factors sections according to grades					
Grade	**n-%**	**Mean ± SD for awareness section**	**Median for awareness section**	**Mean ± SD for risk factors section**	**Median for risk factors section**
1	163-36.5%	43.44 ±20.05	**43.57**	3.77±0.58	**3.84**
2	146-32.7%	47.69 ±21.58	**48.79**	3.64±0.74	**3.79**
3	138-30.9%	75.23 ±17.87	**77.96**	3.80±0.57	**3.90**
Total	**447**	54.64 ±24.25	**54.54**	3.74±0.64	**3.85**
SD: Standard deviation					

Table 5. The mean awareness percentage scores by gender and grade arrangement in the general linear model			
Gender	**Grade**	**Mean**	**Standard error**
Female	1	40.333	8.352
Female	2	44.666	8.481
Female	3	77.558	8.232
Male	1	45.729	7.396
Male	2	53.441	7.278
Male	3	70.000	7.260

dentists are often required to work in uncomfortable postures for extended durations, primarily due to inadequate rest intervals, a situation that significantly increases their risk of developing occupational injuries (9). A study published in 2025 stated that dentists are at great risk due to inappropriate posture and long working hours. In accordance with our results, 76.2% of the participating dentists were found to have poor dental ergonomic practices (4). This study's findings reveal that 61.1% of students lacked knowledge of ergonomics in dentistry. Even when working in ergonomically optimal positions, dentists must maintain static postures that involve the contraction of more than 50% of their muscle groups to counteract gravitational forces. Over time, this can lead to cumulative trauma, muscle imbalances, prolonged repetitive muscle contractions, discomfort, and functional limitations (4,10). The most common symptoms reported among dentists include neck, shoulder, waist, and back pain (11,12). These symptoms may take a considerable amount of time to manifest, and as a result, they are often overlooked until they become chronic and irreversible (13).

The financial implications of work-related musculoskeletal disorders are substantial. These conditions contribute to human resource shortages, high treatment costs, and temporary or permanent work-related deficiencies. work-related musculoskeletal disorders are a major factor driving the early retirement of dentists (14,15). In many industrialized nations, these disorders are considered a significant public health issue, accounting for one-third of all health-related absenteeism (16). A study conducted in our country found that the most negative aspect of the dental profession, as reported by practitioners, was the development of health problems over time, with a prevalence rate of 43% (17). An examination of the general and occupational health of dentists highlights that occupational musculoskeletal diseases are a serious issue, often leading to sick leave and, in severe cases, abandonment of the profession (18). While treatments such as exercise, heat application, and pharmacological therapies are available, preventive measures taken before disease onset are the most effective strategy (19).

Numerous studies have shown that musculoskeletal disorders in dental students typically begin during their academic training (7,20). The prevalence of these disorders among dental students is notably high (21,22). Furthermore, research indicates that although dental students may possess theoretical knowledge of ergonomics, they often fail to apply this knowledge in clinical practice (23,24).

To address this issue, it is recommended that ergonomic patient care habits be cultivated during the earliest stages of education. Early adoption of proper practices can prevent the need for later correction of incorrect posture, a process that is both challenging and time-intensive. With these considerations in mind, the present study aimed to assess the level of ergonomic awareness and knowledge related to occupational diseases among dental students in the preclinical phase. Additionally, it sought to enhance their understanding of these topics before transitioning to clinical practice.

A significant proportion demonstrated limited awareness of critical aspects of dental practice. For instance, 59.3% were unaware of how to work according to a clock-face schedule, 86.4% were unfamiliar with the concept of four-handed dentistry, and 57% displayed limited understanding of occupation-specific musculoskeletal diseases. These results are supported by studies reporting that students actively working in the clinic have a higher awareness of dental ergonomics than students in the preclinical period (24,25). This finding highlights the potential to increase awareness by incorporating occupational ergonomics into the curricula of preclinical students who have yet to begin practical training.

The majority of respondents (79.9%) recognized the role of ergonomics in occupational diseases and work-related accidents. Similarly, 85.5% perceived ergonomics as a factor influencing work efficiency and performance. When all these factors are considered, 56.2% of participants achieved an awareness level exceeding 50%. However, a very low proportion of the students thought that the wrist area would be affected by non-ergonomic work. Furthermore, in support of these data, the majority of the students did not know about carpal tunnel syndrome. These results can be explained by the fact that information about ergonomics and occupational diseases is included at the end of the education curriculum.

The study found a statistically significant positive correlation between students' academic grades and their awareness levels, as measured by percentages and average scores. Our results are in agreement with other studies, which reported that the higher the academic grade of dentistry students, the higher their awareness of pain complaints (24,26). It can be posited that the increase in awareness may be attributed to simulation practice involving patient models, particularly during the 2nd year, and the incorporation of clinical observation elements in the 3rd year of the program. These results suggest that integrating ergonomics into the curriculum and enhancing students' clinical observation skills positively impacts awareness levels.

No statistically significant difference was observed in awareness percentages or means based on gender. However, second-grade males and third-grade females exhibited higher awareness levels. This trend could reflect an overall increase in awareness as students advance academically, combined with the predominance of females in the sample (62.2%).

Similarly, no significant differences in awareness percentages or means were observed across BMI categories. Nevertheless, participants in the obese group had higher average awareness scores. The finding may suggest that increased BMI heightens sensitivity to ergonomic considerations due to movement restrictions and challenges in maintaining proper working conditions. A study published in 2024 reported that BMI was associated with musculoskeletal disorders in dental assistants (26). However, there is also a study reporting that the distribution of BMI is unequal and that BMI is not associated with MSD symptoms (27).

No statistically significant differences were identified in the general risk scale means across academic grades or BMI categories. The absence of a statistically significant difference in risk scale responses among participants who had not yet transitioned to practical applications may be attributed to the fact that the questions pertained more to the potential challenges encountered during the implementation of patient care. The observation that the general risk scale averages are higher in females may reflect the higher physical endurance of males and the more meticulous approach of females to their work environments, potentially enhancing their awareness (28). In addition, many studies have reported that females are more susceptible to musculoskeletal disorders than males (24,27,29).

A significant positive correlation was identified between awareness and risk factors among participants with normal weight, likely reflecting greater knowledge of risks as overall awareness increases; 70.7% of the participants were of normal weight, which may have influenced this finding. Notably, alcohol users demonstrated higher awareness scale averages in this study. Although some studies suggest that alcohol use may be a risk factor for musculoskeletal pain and are consistent with our findings, there is a lack of information on the effect of alcohol use on ergonomic awareness (30). Therefore, given that only 22.1% of participants reported alcohol use, further research with larger samples is needed to draw definitive conclusions.

Study Limitations

Two universities, one public and one foundation, were included in line with accessibility and collaboration opportunities. This study's findings are limited by its focus on preclinical students from two academic faculties, limiting the generalizability of the results. Despite these limitations, the study is useful in raising awareness of ergonomics and occupational musculoskeletal disorders among dental students before they enter clinical practice. It will also provide guidance for the development and organization of training programs. Future research should include more diverse samples and longitudinal studies to better understand the development of ergonomic awareness and its long-term impact on occupational health.

Conclusion

In the absence of an ergonomic work environment, dentists are often compelled to perform tasks that surpass their physical capabilities, inevitably resulting in health complications. It is, therefore, imperative for dental students to be thoroughly aware of the ergonomic risk factors inherent in their workspaces before commencing their clinical placements. These risks can be mitigated by designing work environments that align with ergonomic standards, ensuring that tools and equipment meet appropriate ergonomic criteria, and implementing a well-structured work plan alongside a balanced time schedule.

Given that ergonomic education is typically introduced during the later stages of dental training in

our country, it is essential to integrate this training into the early phases of the clinical patient care curriculum. Early exposure to ergonomic principles will enable students to adopt healthy work habits from the outset of their professional careers, thereby preventing the onset of occupational diseases. Furthermore, this proactive approach will contribute to reducing early retirement rates and the necessity for medical interventions over the long term, ultimately enhancing the efficiency, professional satisfaction, and well-being of dental practitioners.

The findings of this study emphasize the value of embedding ergonomic awareness and education into the foundational stages of dental training. By fostering heightened awareness during the formative years of their education, students will be better equipped to safeguard their health, maintain career longevity, and achieve greater job satisfaction in their future practice.

Ethics

Ethics Committee Approval: Ethical approval for this structured survey study was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University (approval no.: 2024/04-02, date: 18.04.2024).

Informed Consent: Prior to the commencement of the survey, all participants were provided with comprehensive information about the study, and informed consent was obtained through a consent form.

Footnotes

Authorship Contributions

Concept: S.A., Design: S.A., Data Collection or Processing: S.A., I.S.A., Analysis or Interpretation: S.A., I.S.A., Literature Search: S.A., I.S.A., Writing: S.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Assessment of Familial Predisposition Through Parental Inquiry in Undescended Testis Cases

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Abstract

Aim: Non-syndromic cryptorchidism, also referred to as undescended testis (UDT), represents a developmental abnormality occurring in early childhood, the underlying cause of which remains unclear. It is thought to arise from both hereditary susceptibility and environmental influences. This study aimed to explore parental reports concerning familial predisposition (FP) in order to gain further insight into the origins of this frequently encountered and multifactorial condition.

Methods: Between 2012 and 2023, the phone numbers of 1,024 patients who underwent surgery for UDT were retrieved from electronic medical records. The parents of these 1,024 patients were contacted and asked, "Do you or any of your relatives have a diagnosis of udescended testicles (UDT)?" Parents were contacted again via phone 10 days after the initial contact, and the results were recorded in detail. Data from the parents of 823 patients were ultimately incorporated into the study analysis. The collected data were analyzed for FP in terms of dizygotic and monozygotic twins, fathers, siblings, uncles, cousins, and grandfathers.

Results: For the 162 participants identified with FP, the average age was calculated as 4.08±1.87 years. The mean age of the 661 individuals without FP was 3.27±1.80 years. When the relationship between FP and both the localization and laterality of UDT was analyzed, a significant association was found in cases with proximal localization and bilateral involvement ($p<0.05$). Similarly, a significant relationship was observed between FP and genetic predisposition (dizygotic and monozygotic twins) in UDT cases ($p<0.001$).

Conclusion: Our study provides evidence of a connection between non-syndromic cryptorchidism or UDT and FP through a comprehensive evaluation of a large patient series.

Keywords: Cryptorchidism, children, genetic predisposition to disease, parents

Introduction

Cryptorchidism, commonly referred to as undescended testis (UDT) or incomplete descent of testis, represents a frequent congenital anomaly encountered in pediatric urology. Depending on testicular position, cryptorchidism is categorized into cases with palpable and non-palpable testes. Notably, over 80% of cryptorchidism cases involve palpable testes (1). The etiology of UDT remains largely unclear. However, findings suggest that certain cases of cryptorchidism may result from a multifactorial interaction of genetic, anatomical, hormonal, and environmental factors (2). Cryptorchidism associated with chromosomal or developmental anomalies, often as part of syndromic conditions, represents a minor proportion of cases, whereas the majority manifest as isolated UDT (3,4). Although numerous investigations have thoroughly addressed the general epidemiological aspects of UDT, research specifically examining its familial occurrence remains scarce. Important elements such as prevalence rates, potential hereditary correlations, and clinical features, particularly those involving urogenital system anomalies, have not been comprehensively analyzed. The currently available data are mostly derived from studies involving limited sample sizes, often centered around familial relationships like those between fathers, siblings, and twins. Moreover, evidence concerning how common UDT is within the broader population remains limited (5,6).

Undescended testis affects approximately 3-5% of all newborn males and decreases to about 1% in boys by the age of one (7,8). Studies indicate that the likelihood of

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UDT is significantly increased in certain familial situations: a 10.1-fold higher risk in cases where one male twin is affected, 3.5-fold higher in boys with an affected brother, and 2.3-fold higher when the father has UDT (9).

This study is grounded in the assumption that genetic components have an influence on the development of UDT, potentially leading to higher occurrence rates among first-degree family members. The primary objective was to investigate the frequency and pattern of familial predisposition (FP) reported via parental inquiries about relatives, aiming to enhance understanding of UDT origins by utilizing an extensive patient dataset.

Materials and Methods

Compliance with Ethical Standards

The study was approved by the Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approval no.: 25-MOBAEK-015, date: 27.01.2025), adhering to the principles of the Helsinki Declaration.

Study Design

The present study was conducted at a single institution and designed as a retrospective, cross-sectional investigation. Contact details of 1,024 patients who had undergone surgical treatment for UDT at our clinic between 2012 and 2023 were extracted from digital health records. All participants were made aware that their data would be utilized for research purposes, and informed written consent was collected accordingly.

The diagnosis of UDT was confirmed as documented in the physical examination note within the clinical documents. Undescended testis cases were only indicated by the urology clinic. Ultrasonography was not routinely used as previously recommended in the literature (10). Only UDT cases with completely recorded clinical data were included in the study. Cases with a major birth defect, UDT due to a previous hernia surgery, syndromal UDT, or chromosome abnormalities were excluded from the study. According to these criteria, 201 cases were excluded. A total of 823 parents of patients who were successfully contacted by phone and consented to participate in the survey were included in the study. Parents were asked the following question: "Do you or any of your relatives have a diagnosis of UDT?" To ensure accurate responses, they were given 10 days to consult their family members. After 10 days, parents were contacted again via phone. The responses were evaluated for FP in relation to dizygotic and monozygotic twins, fathers, siblings, uncles, cousins, and grandfathers, and carefully recorded for analysis. The flowchart shows the selection of study participants (Figure 1).

Statistical Analysis

All statistical evaluations were carried out using the MedCalc software (version 20.009; Ostend, Belgium). Descriptive analyses encompassed frequencies, ratios, arithmetic means, and standard deviations. Categorical data were examined via the chi-square method, while the Kolmogorov-Smirnov test was applied to assess the normality of the distribution. Comparative group data were visualized through layered percentage bar graphs. A p-value threshold of <0.05 was adopted to determine statistical significance in all interpretations.

Results

The patients analyzed in this study (n=823) were between 1 and 9 years of age. The cohort included 749 unilateral cases and 74 bilateral cases. There were a total of 331 cases with proximal localization and 492 with distal localization. Scrotal (Bianchi) orchiopexy was performed in 244 patients, while inguinal orchiopexy was performed in 579 patients. The mean age of the 162 individuals with FP was 4.08±1.87 years, whereas the mean age of the 661 individuals without FP was 3.27±1.80 years (Table 1).

Among the 162 individuals with FP, UDT was reported in 33 cases, including dizygotic and monozygotic twins, 38 fathers, 26 siblings, 16 cousins, 46 uncles, and 10 grandfathers. Although rare, FP was identified in more than one relative in some cases (Table 2).

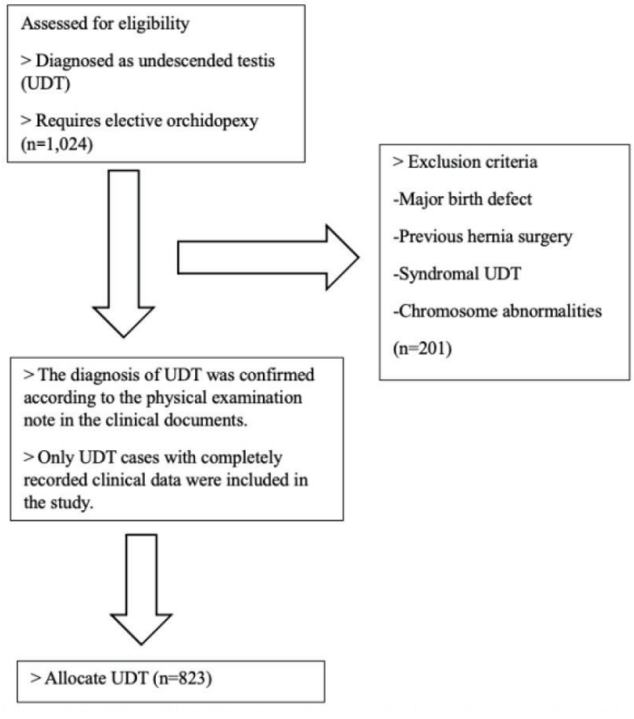

Figure 1. Flowchart shows the selection of study participants
UDT: Undescended testis

When the relationship between FP and UDT localization and laterality was analyzed, a significant association was observed in cases with proximal localization and bilateral involvement ($p<0.05$) (Table 3 and Figures 2, 3). Furthermore, a significant relationship was found between FP and genetic predisposition (dizygotic and monozygotic twins) ($p<0.001$) (Table 3, Figure 4).

Discussion

Familial studies suggest that susceptibility to cryptorchidism is likely influenced by hereditary factors; however, the specific genes responsible for the condition remain unidentified. Some genetic mutations have been associated with syndromic cryptorchidism, although their occurrence in boys with isolated undescended testes is exceptionally rare (11). Research to date, primarily informed by animal model studies, has provided only a limited insight into the etiology of cryptorchidism in humans.

Table 1. Age-related data of individuals with and without familial predisposition

	Familial predisposition					
	Not present			Present		
	n	Mean	SD	n	Mean	SD
Age (year)	661	3.27	1.80	162	4.08	1.87

SD: Standard deviation

Table 2. Distribution of frequencies and percentages in undescended testis cases with familial predisposition

		n	%
Genetic type	**Dizygote**	19	57.6
	Monozygote	14	42.4
Familial proximity	**Father**	38	23.5
	Father&Brother	2	1.2
	Father&Cousins	6	3.7
	Father&Uncle	5	3.1
	Father&Grandfather	2	1.2
	Father&Brother&Uncle	1	0.6
	Father&Cousins&Uncle	1	0.6
	Father&Uncle&Grandfather	2	1.2
	Brother	26	16.0
	Brother&Cousins	1	0.6
	Brother&Uncle	4	2.5
	Brother&Cousins&Uncle	1	0.6
	Cousins	16	9.9
	Uncle	46	28.4
	Uncle&Grandfather	1	0.6
	Grandfather	10	6.2

Most cases of cryptorchidism are non-syndromic, meaning they are not accompanied by other diseases or malformations. Although the underlying causes of non-syndromic cryptorchidism remain largely unknown, numerous medical conditions have been identified in relation to this anomaly (5,11). These include hormonal disorders that impair androgen production or activity, encompassing a wide range of differences in sex development. Such cases may involve impairments in testicular formation or androgen pathways. Both congenital hypogonadotropic and hypergonadotropic hypogonadism have been described, along with syndromes affecting either or both stages of gonadal function. Additionally, alterations in the levels or biological activity of regulatory peptides like INSL3 or AMH have been potentially implicated (12,13). Cryptorchidism has been linked to over 150 comorbid conditions, including

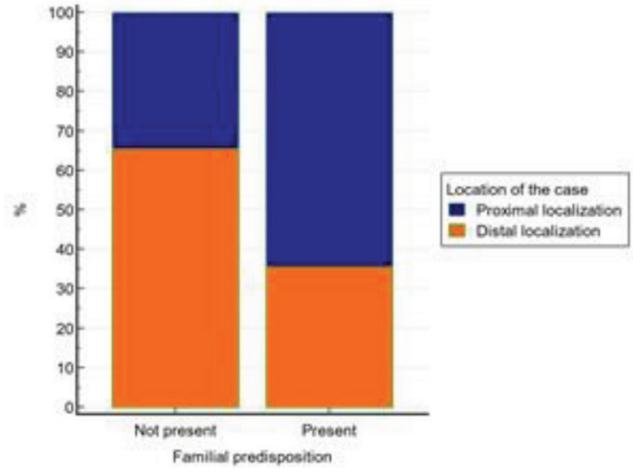

Figure 2. The Relationship between familial predisposition and the localization of undescended testis

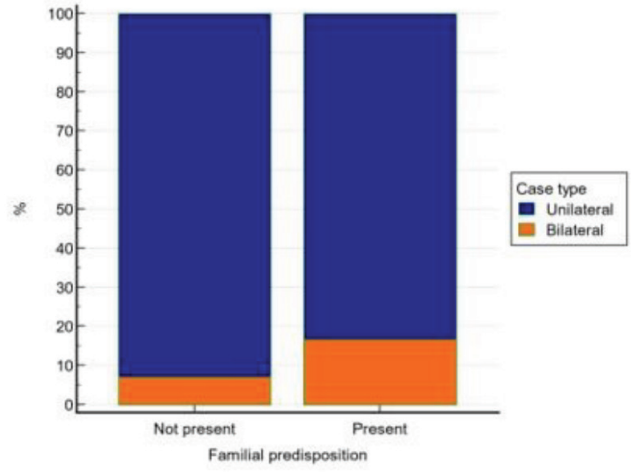

Figure 3. The Relationship between familial predisposition and the laterality of undescended testis

cardiovascular, reproductive, ophthalmologic, mental, dermatologic, and skeletal disorders, as well as hearing loss and cancer (14). The most commonly reported comorbidity of cryptorchidism is hypospadias (5,14). Consequently, several genomic variations have been implicated in the pathogenesis of cryptorchidism. Boys with UDT tend to have a higher prevalence of a positive family history for cryptorchidism compared to healthy controls. Previous research indicates that approximately 7% of their brothers may also be affected (15). Data from Denmark revealed varying concordance rates: 3.2% among unrelated boys, 3.4% in paternal half-siblings, 6.0% in maternal half-siblings, and 8.8% among full siblings. The rate was notably higher-around 25%-in both dizygotic and monozygotic twin pairs. These observations highlight the potential influence of shared intrauterine conditions, particularly in twin pregnancies (16). In a retrospective analysis of 165 children who underwent surgery for UDT, Bjøro K and Dybvik (17) reported that 3.9% of fathers and 6.5% of brothers were also affected by it.

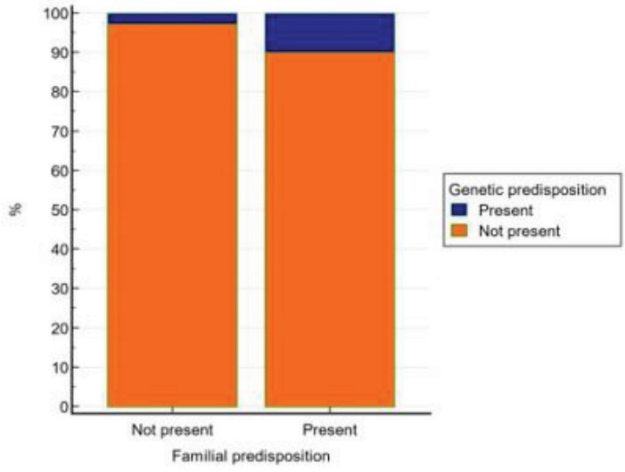

Figure 4. The Relationship between familial predisposition and genetic predisposition

In a separate investigation, Jones and Young (18) analyzed the family histories of 51 children who had undergone similar procedures, identifying UDT in 3.9% of fathers, 9.8% of brothers, and 10.6% of uncles.

Czeizel et al. (19) conducted the only available epidemiological research in this area and noted UDT in 3.98% of fathers and 6.2% of brothers within the affected group. The likelihood of UDT in male infants born into families with known cases was notably higher, up to fivefold when the father is affected and reaching an eightfold increase if a brother is also affected by the condition. Elert et al. (20) demonstrated that while familial clustering was rare, cryptorchidism occurred much more frequently among family members of affected individuals (23%) compared to the control group (7.5%). These findings suggest the presence of genetic risk factors for cryptorchidism.

Similar to other complex diseases, multiple genetic variants are likely to contribute to susceptibility to this condition. Moreover, current research indicates that male offspring and brothers of individuals diagnosed with cryptorchidism are more likely to develop the same condition. Several studies have pointed out that the likelihood of familial transmission tends to decline as genetic relatedness becomes more distant (20-24). For example, Jensen et al. (16) and Schnack et al. (25) identified notably higher concordance rates in maternal half-brothers (6%) when compared to paternal half-brothers (3.4%). Drawing upon these insights, including findings from twin studies, researchers have proposed that future investigations into etiology should prioritize maternal genetic pathways, especially those linked to the X chromosome and factors within the intrauterine environment (25). On the other hand, bilateral cryptorchidism is observed in approximately 10% of all patients with UDT (26). Bilateral undescended testes correlate with an increased risk of infertility and testicular malignancy (27). Prevalence rates exhibit significant regional variations, influenced by environmental, socioeconomic, and genetic factors.

Table 3. The relationship between familial predisposition and localization, laterality, and genetic predisposition of undescended testis

		Familial predisposition				p-value
		Not present		Present		
		n	%	n	%	
Location of the case	**Distal localization**	434	65.7	58	35.8	<0.0001*
	Proximal localization	227	34.3	104	64.2	
Case type	**Bilateral**	47	7.1	27	16.7	0.0001*
	Unilateral	614	92.9	135	83.3	
Genetic predisposition	**Not present**	644	97.4	146	90.1	<0.0001*
	Present	17	2.6	16	9.9	

*Chi-square test results indicate a significant difference at the <0.05 level

However, only a few published studies have focused specifically on the genetic background of undescended testes. According to findings by Czeizel et al. (19), bilateral cases appear to be linked with an elevated risk of recurrence among siblings. The same research also indicated that individuals with bilateral undescended testes had fathers and brothers who were twice as likely to be diagnosed with the condition (19). In another study, 12.2% of patients with bilateral UDT were found to have family relationships with UDT (20). In our study, it was observed that 16.7% of bilateral UDS familial factors were positive. Similarly, in our study, we observed a FP for UDT in proximal localization, which has negative effects on fertility.

We believe that our study contributes valuable insights into the association between UDT and FP. The large sample size enabled the generation of robust statistical data. The analysis of familial relationships was not limited to fathers and siblings but extended to various degrees of relatives. Among the 162 individuals with FP, for instance, UDT was observed in 20% of dizygotic and monozygotic twins, 23.5% of fathers, 16% of siblings, 9.9% of cousins, 28.4% of uncles, and 6.2% of grandfathers. FP was also identified in multiple relatives in some cases, albeit infrequently. The high prevalence observed in our study may be attributed to the large sample size and potential genetic variations. Additionally, our findings demonstrate that FP is more frequently observed when UDT localization is proximal and/or bilateral, and the likelihood increases with a greater prevalence of dizygotic and monozygotic twins. While FP in dizygotic and monozygotic twins is a known factor, the significant increase in FP in bilateral and/or proximally localized cases is a noteworthy finding. We could not determine a clear preference for paternal or maternal inheritance in this study. Therefore, the reasons for the higher prevalence of familial UDT remain uncertain. Potential chromosomal microdeletions, genetic susceptibilities in testosterone-sensitive organs, and/or environmental cofactors should be further explored and discussed.

Study Limitations

The primary limitations of this study include the subjectivity of survey-based data, the unknown impact of genetic and environmental factors on the study's outcomes, and its single-center, regionally focused design. On the other hand, since the data used in a part of our study was obtained by phone calls, we may encounter "recall bias", where respondents may incorrectly remember details when answering. This is another important limitation of our study. Despite these limitations, detailed determination of the pedigrees of cases with UDT is the strength of our study.

Conclusion

A comprehensive analysis of a large family cohort revealed a higher incidence of UDT than previously reported in the literature. Furthermore, our study demonstrated that FP is more frequently observed when UDT localization is proximal and/or bilateral, and its prevalence increases with a higher occurrence of dizygotic and monozygotic twins. It is anticipated that molecular analyses could provide further insights into the genetics of UDT, serving as a focal point for future research.

Ethics

Ethics Committee Approval: The study was approved by Tokat Gaziosmanpasa University Faculty of Medicine Clinical Research Ethics Committee (approvel no.: 25-MOBAEK-015, date: 27.01.2025) adhering to the principles of the Helsinki Declaration.

Informed Consent: Patients were informed that their data would be used for scientific purposes, and written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Y., E.K., F.F., Concept: K.Y., E.K., F.F., Design: K.Y., E.K., F.F., Data Collection or Processing: K.Y., E.K., F.F., Analysis or Interpretation: K.Y., E.K., F.F., Literature Search: K.Y., E.K., F.F., Writing K.Y., E.K., F.F.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Clinical and Endoscopic Outcomes of De Meester Switch in Duodenogastric Alkaline Reflux Disease: A Retrospective Analysis with Mid-Term Follow-up

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Abstract

Aim: By presenting endoscopic, symptomatic, and quality-of-life outcomes with mid-term follow-up, this study aims to contribute to the limited body of evidence regarding the results of the De Meester Switch method for duodenogastric alkaline reflux disease (DGAR-D).

Methods: Between 2017 and 2023, laparoscopic De Meester Switch surgery was performed on 30 patients with DGAR-D symptoms for over three years. The total bilirubin (TB) and direct bilirubin (DB) levels were measured in the gastric reflux content and serum at baseline and the last follow-up. In addition, the patient's baseline and postoperative DGAR-D symptoms were evaluated in the sixth, twelfth, and last follow-up months. The Reflux Disease Questionnaire (RDQ) was used retrospectively to assess the patient's quality of life.

Results: Before surgery, most patients experienced nausea (76.6%), epigastric pain (80%), bloating (90%), heartburn (76.6%), bilious vomiting (56.6%), and sore throat (53.3%). Moreover, 93.3% of those who endured these symptoms for 3-12 years found no relief with medical treatment. Post-surgery, all symptoms significantly decreased ($p<0.001$). At a 34-month follow-up, some experienced persistent nausea and bloating (13.3%), epigastric pain (20%), heartburn, and sore throat (6.6%). However, bilious vomiting and biliary intestinal fluid stasis resolved entirely (100%). Preoperative gastric aspirate TB and DB levels were 2.4 and 2.1 mg/dL, respectively, reducing to 0.4 and 0.2 mg/dL postoperatively. The RDQ score significantly decreased from 82.21±3.10 to 31.13±3.09 at the last follow-up, with no observed mortality.

Conclusion: The De Meester Switch can prevent the reflux of bilious duodenal contents into the stomach in patients with DGAR-D and significantly reduce complaints. This treatment is safe and effective when applied laparoscopically.

Keywords: Duodenogastric reflux, bile reflux, gastroesophageal reflux disease (GERD), dyspepsia

Introduction

Duodenogastric alkaline reflux (DGAR) is characterized by the retrograde flow of bile and pancreatic secretions into the stomach and esophagus. This condition is often associated with symptoms such as epigastric pain, bloating, nausea, and bile vomiting, and in more severe cases, may lead to bile-induced gastritis or contribute to gastroesophageal reflux disease (GERD) (1). Despite its clinical impact, DGAR remains a relatively underrecognized and underdiagnosed entity, with no established consensus on diagnostic criteria or optimal management strategies (2).

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Gastroesophageal reflux disease can be particularly debilitating in patients who suffer from persistent symptoms despite acid-suppressive therapy. While medical options such as prokinetics and bile acid binders may provide some relief, they often fail in cases of severe bile reflux (3). Surgical diversion of bile away from the stomach represents a physiologically rational approach, aiming to eliminate duodenal refluxate from the gastric reservoir and alleviate mucosal injury. This concept was first introduced in 1987 by MD. Tom R. DeMeester, who described the "DeMeester Switch" procedure as a bile diversion technique for medically refractory reflux disease (4). Based on our clinical experience with patients who underwent De Meester Switch surgery for intractable bile reflux, we retrospectively examined whether this surgical technique could provide symptom relief and endoscopic improvement.

Although no prospective hypothesis was formulated at the outset, the present study was conducted to retrospectively evaluate the outcomes of bile diversion surgery in patients with confirmed duodenogastric bile reflux who remained symptomatic despite medical therapy. By presenting endoscopic, symptomatic, and quality-of-life outcomes with mid-term follow-up, this study aims to contribute to the limited body of evidence regarding surgical treatment options for this challenging condition.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (approval no.: 01/06, date: 09.01.2023). Informed consent was obtained from all individual participants included in the study. Data were collected retrospectively and anonymized prior to analysis to ensure patient confidentiality.

Study Design

The study included 30 patients who underwent surgery between June 2017 and September 2023, all of whom had been symptomatic for more than three years. Endoscopic evaluations revealed severe bile loculations in their stomachs (Figure 1), indicative of DGAR-disease

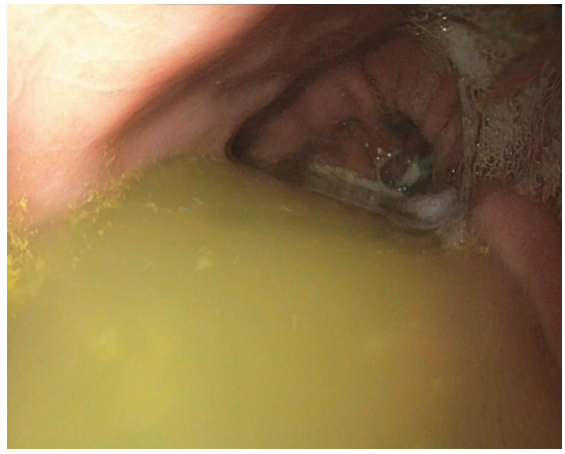

Figure 1. A typical "Bile Lake" formation in a patient with duodenogastric alkaline reflux disease

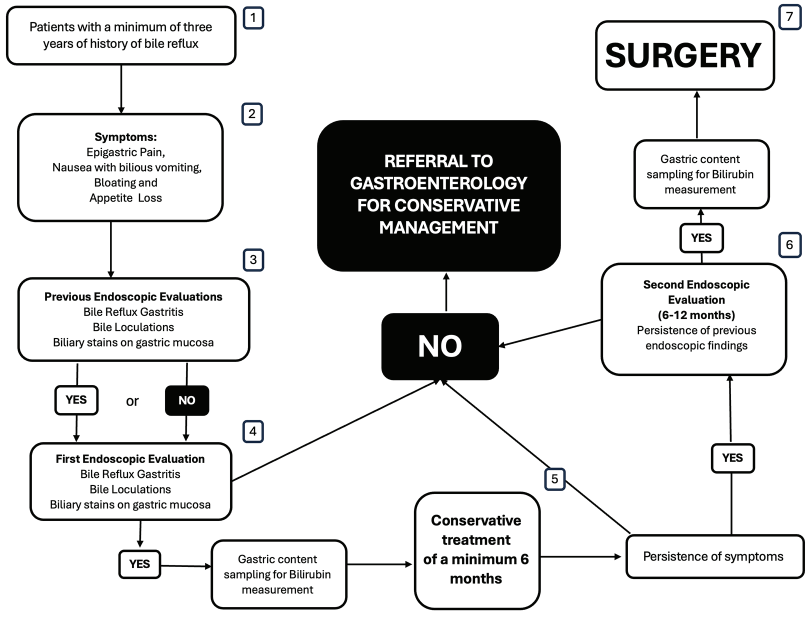

Figure 2. The flowchart diagram of the diagnosis of the patients

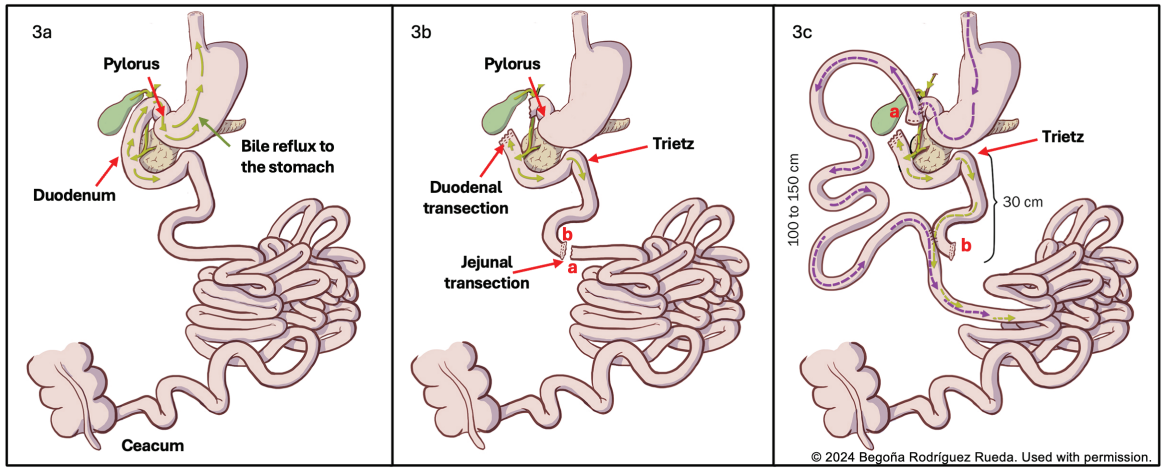

Figure 3. The steps of surgical technique. The duodenum is transected 2-3 cm away from the pylorus, and the proximal jejunum is divided at 30 cm to the Treitz ligament. A hand-sewn duodenojejunal anastomosis is performed between the distal tip of the jejunum (b) and the post-pyloric duodenum. The tip of the biliopancreatic loop (a) is anastomosed to the alimentary limb at 100-150 cm distal to the duodenojejunostomy in a side-to-side fashion with a vascular stapler

(DGAR-D). Despite prior medical and nutritional support, the patients required 6-12 months of monitoring with dietary adjustments and medical therapy, with two endoscopies per patient. Total bilirubin (TB) and direct bilirubin (DB) levels were measured in gastric aspirates and blood samples. Surgery was considered if severe bile stasis persisted in subsequent endoscopies. All patients were regularly monitored postoperatively, with an endoscopic follow-up at 6-18 months. Results were evaluated retrospectively. The flowchart for the diagnosis of patients is given in Figure 2.

Surgical Technique

The procedure was laparoscopic and performed under general anesthesia. Patients were placed supine, and their legs were split in the French position. Four ports were used for surgery. The duodenum was dissected and isolated until the gastroduodenal artery was seen near the pancreatic head. The duodenal transection was done with 2.5 mm vascular white cartridges. The stump was not buried with sutures. The jejunum was measured from the non-stretched anti-mesenteric wall and transected with 2.5 mm vascular white cartridges at 30 cm from the Treitz ligament. The distal tip of the jejunal loop (the Roux limb) was pulled up in an antecolic fashion, and a laparoscopic hand-sewn duodenojejunostomy was performed intracorporeally. The integrity of the anastomosis was checked by filling the distal stomach with a blue dye solution while clamping the proximal stomach and the jejunal loop distal to the anastomosis. The proximal tip of the transected jejunum (the biliopancreatic limb) was anastomosed to the Roux limb with a 2.5 mm vascular white cartridge at 100 cm distal to duodeno-jejunostomy. Mesenteric defects were closed by placing separate stitches with non-absorbable monofilament sutures. One suction drain was placed under the duodeno-jejunostomy, extending to the transected duodenal stump. All port sides were closed with non-absorbable sutures (the steps are demonstrated in Figure 3).

Reflux Disease Questionnaire

Reflux Disease Questionnaire (RDQ) is a questionnaire consisting of 12 questions, developed by Shaw et al. (5). Hançerlioğlu and Bor (6) conducted a Turkish reliability and validity study of the survey. Cronbach's alpha of the survey was found to be 0.92. Half of the questions were related to the severity of symptoms, while the other half pertained to their frequency, with both measured on a 6-point scale (from no occurrence to daily/severe). As the score increases, so does the severity of the disease.

Statistical Analysis

Statistical analysis was performed using SPSS 20 software. The Shapiro-Wilk test was used to evaluate the suitability of the measured data for a normal distribution. Mean, standard error, minimum, and maximum values of continuous variables and frequency and percentage values of categorical variables were given. The Wilcoxon test was applied to compare continuous data. The Cochran Q test was used to compare categorical data. The McNemar test was applied for pairwise comparisons. For statistical analysis results, a p-value of less than 0.05 was considered significant.

Results

Demographic and baseline clinical data are summarized in Table 1. The cohort consisted of 22 female and 8 male

patients with a mean age of 40.9 years. The average duration of symptoms was 6 years, and the mean follow-up time was 34.3 months. Two patients (6.7%) experienced postoperative complications requiring surgical revision.

The Wilcoxon test demonstrated statistically significant reductions in RDQ scores (p<0.001), reflux TB (p<0.001), and reflux DB (p<0.001) levels following surgery. Serum DB levels showed a significant postoperative increase (p=0.017), while changes in serum TB were not statistically significant (Table 2).

Symptom resolution was assessed across multiple timepoints using the Cochran Q and McNemar tests. Significant improvements were observed postoperatively in nausea, bilious vomiting, epigastric pain, bloating, heartburn, sore throat, and unresponsiveness to medical treatment (all p<0.001). Additionally, bile lakes, which were present in all patients preoperatively, were no longer detected at the final endoscopic follow-up (p<0.001) (Table 3).

Table 1. Demographic data of the patients

Variables		**Mean±SD (Minimum-Maximum)**
Age, year		40.86±13.05 (19-63)
Average duration of symptoms		6.30±2.18 (3-12)
Average last follow-up time, month		34.33±24.47 (5-79)
Average endoscopy time after surgery, month		7.73±4.09 (3-18)
Surgery duration, minutes		104.46±26.88 (68-189)
Stay at hospital, day		4.10±1.02 (3-7)
Irritable bowel syndrome		**n (%)**
	No	24 (80%)
	Yes	6 (20%)
Small intestine bacterial overgrowth		
	No	29 (96.7%)
	Yes	1 (3.3%)
Complication		
	No	28 (93.3%)
	Yes	2 (6.7%)
Previous cholecystectomy		
	No	11 (36.7%)
	Yes	19 (63.3%)
Simultaneous surgery		
	No	19 (63.3%)
	Cholecystectomy	10 (33.4%)
	Nissen fundoplication	1 (3.3%)
Second surgery		
	No	30 (93.3%)
	Yes	2 (6.7%)

SD: Standard deviation

Table 2. Comparison of some parameters of the patients before and after the operation

	Preop	**Postop**	**z**	**p-value**
RDQ	82.21±3.10 (30.5-100)	31.13±3.09 (16.7-76.4)	**-4,782**	**<0.001**
Serum total bilirubin	0.55±0.30 (0.3-2.0)	0.55±0.13 (0.4-0.9)	-0.913	0.361
Serum direct bilirubin	0.20±0.17 (0.1-1)	0.25±0.09 (0.1-0.5)	**-2,384**	**0.017**
Reflux total bilirubin	2.41±0.50 (1.3-3.7)	0.39±0.14 (02.-0.7)	**-4.,786**	**<0.001**
Reflux direct bilirubin	2.09±0.49 (0.9-3.1)	0.15±0.08 (0-0.4)	**-4,786**	**<0.001**

z: Wilcoxon test
RDQ: Reflux Disease Questionnaire

Discussion

In this study, we performed our modified De Meester Switch method on 30 patients diagnosed with DGAR-D. A significant decrease in DGAR-D symptoms was observed from the sixth month after surgery. All patients had control endoscopies within the first 18 months after surgery, and no biliary intestinal content was present in any of the patients.

Table 3. Comparison of different parameters of patients before and after surgery

	No	Yes	df	Cohran's Q value	p-value
Nausea					
Baseline	7 (23.3%)	23 (76.7%)	3	**46,800**	**<0.001***
Sixth month	22(73.3%)	8 (26.7%)			
Twelfth month	25 (83.3%)	5 (16.7%)			
Last follow-up	26 (86.7%)	4 (13.3%)			
Bilious vomiting					
Baseline	13 (43.3%)	17 (56.7%)	3	**51,000**	**<0.001***
Sixth month	30 (100%)	0 (0%)			
Twelfth month	30 (100%)	0 (0%)			
Last follow-up	30 (100%)	0 (0%)			
Epigastric pain					
Baseline	6 (20%)	24 (80%)	3	**39,563**	**<0.001***
Sixth month	22 (73.3%)	8 (26.7%)			
Twelfth month	22 (73.3%)	8 (26.7%)			
Last follow-up	24 (80%)	6 (20%)			
Bloating					
Baseline	3 (10%)	27 (90%)	3	**53,415**	**<0.001***
Sixth month	25 (83.3%)	5 (16.7%)			
Twelfth month	26 (86.7%)	4 (13.3%)			
Last follow-up	26 (86.7%)	4 (13.3%)			
Unresponsiveness to medical treatment					
Baseline	2 (6.7%)	28 (93.3%)	3	**58,443**	**<0.001***
Sixth month	23 (76.7%)	7 (23.3%)			
Twelfth month	23 (76.7%)	7 (23.3%)			
Last follow-up	27 (90%)	3 (10%)			
Heartburn					
Baseline	7 (23.3%)	23 (76.7%)	3	**54,000**	**<0.001***
Sixth month	25 (83.3%)	5 (16.7%)			
Twelfth month	28 (93.3%)	2(6.7%)			
Last follow-up	28 (93.3%)	2 (6.7%)			
Sore throat					
Baseline	14 (46.7%)	16 (53.3%)	3	**32,872**	**<0.001***
Sixth month	26 (86.7%)	4 (13.3%)			
Twelfth month	27 (90%)	3 (10%)			
Last follow-up	28 (93.3%)	2 (6.7%)			
Bile lakes				**X^2**	**p-value**
Baseline	0 (0%)	30 (100%)		**28,033**	**<0.001¥**
Last follow-up	30 (100%)	0 (0%)			

*Cochran Q test, ¥McNemar test

Bile can cause severe mucosal damage when in contact with gastric, esophageal, and even laryngopharyngeal regions, and has been implicated in various diseases such as gastric polyps, chronic atrophic gastritis, peptic ulcers, pernicious anemia, erosive esophagitis, Barrett's esophagitis (dysplasia), post-cholecystectomy syndrome/ reflux, and gastricr (1,7). A recent study found a strong correlation between the quality-of-life (QoL) reflux symptom score and salivary bile salts in patients with laryngopharyngeal reflux disease-related chronic cough. Patients with chronic cough exhibited more severe symptoms than those without, and salivary elastase and bile salts were identified as potential predictors of clinical findings (8).

The clinical presentation of DGAR-D is similar to that of GERD. However, the efficacy of lifestyle modification and medical treatment is controversial in the literature for DGAR. Proton pump inhibitors (PPIs) were compared in symptomatic and asymptomatic GERD patients who had accompanying DGAR, and no statistical significance was found for the healing effect of PPI (9). Five out of 223 DGAR patients who did not respond to PPI treatments were found to have bile lakes in their stomach (10).

Ursodeoxycholic acid therapy was shown to reduce biliary reflux significantly and associated gastritis after distal gastrectomy with Billroth-I reconstruction by approximately 50% at 12 months postoperatively, compared to placebo (11). However, there has been no established consensus or treatment algorithm for DGAR.

The patients in our study had severe symptoms, with 76.6% experiencing nausea, 80% experiencing epigastric pain, 90% experiencing bloating, 76.6% experiencing heartburn, 56.6% experiencing bilious vomiting, and 53.3% experiencing sore throat. In addition, it was found that 93.3% of the patients, who had been suffering from these symptoms for 3-12 years, did not respond to medical treatment.

Elhak et al. (12) achieved a significant control rate of symptoms in patients with DGAR-associated distal esophagitis via medical treatment, up to 70.8%. However, while the presence of bile in the stomach of these patients was detected via an impedance pH meter and spectrophotometric analysis with Bilitec 2000, there was no observable bile stasis in endoscopy, and the high response rate to medical therapy was attributed to the absence of bile lakes in the patients' stomachs (12). In our study, bile lakes were detected during endoscopy in all patients, and the high rate of non-response to medical treatment, over 93 percent, may be related to their presence in these patients.

Unresponsiveness to medical treatment is the main indication for surgical treatment. However, the diagnosis and symptomatology of the disease, and when and what type of surgery to perform, are still controversial. There is no consensus on any of these aspects concerning DAGR-D. Having a history of more than one year of symptoms and unresponsiveness to medical and nutritional treatments is fundamental for most studies in the literature. Truncal vagotomy, antrectomy, and Roux-en-Y gastro-jejunostomy are the most preferred surgical methods to treat alkaline reflux.

This is mainly related to the familiarity of most surgeons with the technique and the simplicity of the procedure compared to the duodenal switch. The De Meester Switch, when performed laparoscopically, is a technically complicated procedure, requiring the dissection and transection of the duodenum in precarious anatomical areas and advanced skills to perform an intracorporal anastomosis. However, it is more physiological to preserve the integrity of the stomach and pylorus rather than gastrectomy with Roux-n-Y gastrojejunostomy. The choosing Nissen fundoplication for GER with accompanying biliary reflux may overlook the significant pathology underlying most symptoms. The surgeon involved in this study had completed more than 500 variations of switch surgeries.

The candidates for surgery in this study were not the patients with trace amounts of biliary presence in the stomach that can be detected only by the impedance-pH meter. Rather, they had persistent and severe bile lakes consistently observed on serial endoscopic examinations over a prolonged period, specifically for at least three years, within a mean symptom duration of six years (range: 3-12 years).

All procedures were completed laparoscopically without any mortality. Only two patients were re-operated on for surgery-related complications. Both underwent antrectomy and Roux-en-Y gastrojejunostomy. Our study showed that the rate of postoperative symptoms in patients decreased significantly compared to the preoperative period. All patients had endoscopic evaluation at least once after surgery, and no bile was observed in any follow-up endoscopies. Although there was an absence of bile in postoperative endoscopies and a statistically significant decrease in unresponsiveness to medical treatments (99.3% in pre-op and 23.3% in postoperative 6 and 12 months), it is essential to observe that despite a complete diversion of bile from the stomach, still one out of five patients had no relief of symptoms in our cohort. Klingler et al. (13) reported a significant reduction in clinical symptoms in 94% of 32 patients with De Meester Switch for primary DGAR. del Genio et al. (14) reported total relief of symptoms in two cases after the De Meester Switch. Both patients had severe bile lakes in the stomach, which completely resolved after surgical treatment. Strignano et

al. (15) reported that after the duodenal switch procedure, 44 of 48 patients were satisfied with the surgery, while four were dissatisfied. Dumping syndrome occurred in one of these four patients, the complaints did not improve in two, and a recurrence was observed in another after a long follow-up. In the patient with recurrence, the 60 cm Roux-en-Y jejunal loop was extended to 110 cm, and symptomatic improvement was achieved. The reason some of the symptoms persisted in some patients in our study may be related to the longer duration of DGAR-D and the severe clinical symptoms of our patients due to the selection criteria for surgery.

In patients included in this study, the gastric contents obtained from aspiration, with bile seen during endoscopy, revealed TB levels of 2.4 mg/dL and DB of 2.1 mg/dL. Chen et al.'s (16) study determined that gastric bile acid levels of DGR patients were significantly higher than control values (TB; 5.49 vs. 1.63; DB; 5.43 vs. 1.87). Although the bilirubin levels in the gastric contents detected in our study were significantly higher than those in simultaneously collected serum samples, they were observed to be lower than data reported in other studies. A study investigating bile reflux in patients undergoing one anastomosis gastric bypass (OAGB) reported bilirubin levels in gastric contents up to 27 mg/dL (17). However, normal levels were also reported in some patients. Another study reported higher bilirubin levels in gastric aspirate (7 and 11.3 mg/dL) than in the duodenum (<5 mg/dL) when an underlying intestinal obstruction was present (18). In our study, lower bilirubin levels, compared to patients with OAGB, may have been due to our patients' preservation of gastric integrity and residual bile in the stomach. In individuals with primary DGAR, bile may remain in the stomach longer, increasing the likelihood of dilution with gastric and salivary secretions. In patients with OAGB, however, the reduced gastric volume (between 50-100 cc) may prevent bile retention in the stomach. This led to a higher probability of sampled bile quickly refluxing from the intestines to the stomach. Additionally, decreased gastric secretion in the reduced stomach may explain a more concentrated bile content in the stomach. Although the bilirubin levels in gastric aspirate were lower in our study group compared to other studies, they returned to normal levels after surgery.

Our study retrospectively evaluated patients' preoperative complaints using the RDQ during the final follow-up period (average 34 months). Simultaneously, we administered the same questionnaire again to assess their complaints. Our results showed a statistically significant decrease in the RDQ score after surgery, thus being associated with a significant increase in their quality of life. Given the retrospective nature of our study, one methodological constraint is the post hoc administration of the RDQ, which introduces a potential for recall bias. Patients were asked to evaluate their preoperative symptom burden an average of more than two years after their surgery, which may have affected the accuracy of recollection, particularly for subjective symptoms such as pain, bloating, and heartburn. While recall bias is a recognized issue in retrospective quality-of-life research, mainly when current health status influences perceptions of past symptoms (19), the RDQ - a validated and reliable instrument (5,6) - still provided a structured and standardized means of capturing symptomatic change. Prospective symptom tracking with pre- and post-operative RDQ administration would be ideal for future studies to quantify treatment efficacy and minimize bias with greater precision.

Study Limitations

Our study has several limitations. First, the study was conducted retrospectively and included a relatively small number of patients, which may limit the statistical power and generalizability of the results. Not all patients had long-term follow-ups beyond 18 months, thus preventing comprehensive long-term evaluation of outcomes.

The absence of a control group further limits our ability to directly compare outcomes with other treatment modalities or the disease's natural course. This limitation is inherent to the study's retrospective design; patients were operated on based on clinical indications, without the intention to conduct a prospective trial. For the same reason, preoperative RDQ assessments were not routinely performed before surgery but were administered retrospectively. This approach introduces a potential for recall bias, as patients may not accurately recall the frequency and severity of symptoms experienced before surgery.

Lastly, although bile lakes in the stomach were demonstrated and sampled endoscopically in all patients and bilirubin levels were measured to confirm the presence of bile, we could not use Bilitec 2000 spectrophotometry or hepatobiliary scintigraphy to further evaluate bile reflux due to the limited availability of these technologies in our country.

Despite these limitations, the strength of our study is that the cohort of patients had severe symptoms with long durations, the patients' endoscopic diagnoses were well-defined with the presence of bile lakes in all patients, and the valid and reliable RDQ was used to evaluate their quality of life. Another strength of our study is its contribution to literature, as there are scarce reports of the De Meester Switch procedure for DGAR. Our study provides significant efficacy in preventing bile reflux, alleviating symptoms of the patients, and increasing QoL.

Conclusion

Our study determined that the modified De Meester Switch Surgery significantly reduced the symptoms and improved the patients' quality of life with DGAR-D. Laparoscopic application of the De Meester Switch Surgery is a highly complicated procedure and may lead to severe complications. However, it can be performed safely by experienced surgical teams. Switch surgery has significant physiological advantages over gastrectomy and Roux-en-Y gastrojejunostomy, especially in preventing dumping syndrome by preserving the stomach and the pylorus valve.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Trakya University Faculty of Medicine Non-Interventional Scientific Research Ethics Committee (approval no.: 01/06, date: 09.01.2023).

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

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Footnotes

Authorship Contributions

Surgical and Medical Practices: T.D., Z.T., S.U., Concept: T.D., S.U., Design: T.D., S.U., Data Collection or Processing: T.D., Z.T., Analysis or Interpretation: T.D., Z.T., S.U., Literature Search: T.D., Z.T., Writing: T.D., Z.T., S.U.

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Original Article

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Efficacy of Transcatheter Arterial Embolization in Managing Rectus Sheath Hematoma: A Tertiary Single Center Results

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Abstract

Aim: Rectus sheath hematoma (RSH) is a rare but potentially life-threatening condition. This study aimed to evaluate the effectiveness of transcatheter arterial embolization (TAE) in the management of RSH by analyzing imaging features, embolization techniques, and clinical outcomes.

Methods: In this retrospective observational study, 22 patients with RSH who underwent TAE between June 2020 and June 2023 were included. Etiological factors, hematoma classification, angiographic findings, embolization materials, and clinical outcomes were analyzed. Laboratory values and transfusion requirements were compared before and after the procedure.

Results: The most common etiology was anticoagulation therapy (50%), followed by trauma (13.6%) and post-abdominal surgery (13.6%). A bleeding source was identified in 36.3% of patients on computed tomography angiography and 45.4% on digital subtraction angiography. Technical success was 100%, and clinical success was 90.9%. Post-embolization, transfusion requirements decreased significantly ($p<0.05$). Hemoglobin and hematocrit levels increased by 17.2% ($p=0.004$) and 20.7% ($p=0.001$), respectively. No significant difference was observed between Type 2 and Type 3 hematomas in terms of clinical and procedural outcomes.

Conclusion: TAE is a safe and highly effective treatment for RSH, leading to significant hemodynamic stabilization and reduced transfusion requirements. It should be considered a primary treatment option in patients with moderate to severe RSH, particularly those who are hemodynamically unstable.

Keywords: Rectus sheath hematoma, interventional radiology, embolization, epigastric artery

Introduction

Rectus sheath hematoma (RSH) is a rare but serious condition where there is bleeding in the covering of the rectus abdominis muscle, usually caused by a tear in the superior or inferior epigastric arteries or an injury to the muscle itself. Common predisposing factors include anticoagulant therapy, trauma, and conditions that increase intra-abdominal pressure, such as coughing, straining, or pregnancy. While the majority of RSH cases are self-limiting and managed conservatively, severe hemorrhage can lead to hemodynamic instability, necessitating urgent intervention (1,2). With the widespread use of anticoagulants and the aging population, the incidence of spontaneous RSH has been increasing. Cross-sectional imaging, particularly contrast-enhanced computed tomography (CT), plays a pivotal role in diagnosing RSH,

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assessing hematoma extent, and detecting active bleeding (3). In hemodynamically unstable patients or those with ongoing hemorrhage, endovascular approaches such as transcatheter arterial embolization (TAE) have emerged as safe and effective alternatives to surgery, offering high technical success with minimal invasiveness (4,5).

Although TAE has been widely adopted for managing spontaneous soft tissue hematomas, data specifically focusing on its efficacy in RSH remain limited, with most studies comprising small patient cohorts and heterogeneous bleeding etiologies (2,6). Moreover, the impact of embolization techniques, choice of embolic agents, and the predictive value of imaging findings on clinical outcomes are yet to be clearly defined in this subset of patients (7-9). We hypothesized that TAE achieves a highly effective and safe treatment modality for managing RSH with high technical and clinical success rates, regardless of hematoma type or the presence of angiographic active bleeding.

The primary aim of this study was to evaluate the imaging characteristics, embolization techniques, and clinical outcomes of patients with RSH who underwent TAE at our institution over a four-year period. By providing detailed procedural and clinical data, this study aims to contribute to the optimization of endovascular management strategies for RSH. This, in turn, is expected to facilitate timely intervention, reduce transfusion requirements, and improve patient outcomes in clinical practice.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital Ethics Committee (approval no.: 130, date: 24.07.2024). As this was a retrospective study based on anonymized data, the requirement for informed consent was waived by the ethics committee.

Study Population

In this retrospective observational study, medical records of patients diagnosed with RSH and treated with TAE in our department between June 2020 and June 2023 were reviewed. The patient selection process is summarized in Figure 1.

Inclusion Criteria

- Development of RSH during anticoagulation therapy.
- Iatrogenic RSH
- Decreased hemoglobin/hematocrit levels due to RSH, requiring blood transfusion.
- Age ≥18 years.
- Availability of medical records and cross-sectional imaging.

Exclusion Criteria

- Patients with RSH who did not undergo endovascular treatment and were managed conservatively.
- Unavailable medical records and cross-sectional imaging.
- Patients referred from an external center for the procedure who were lost to follow-up at our institution, with unavailable follow-up laboratory values and clinical data.
- Patients with multiple trauma where the primary bleeding site was outside the rectus sheath, such as in the spleen or liver.

Data Collection and Analysis

Clinical and radiological variables were recorded in a dedicated dataset, including age, RSH etiology (spontaneous, traumatic, post-endovascular transfemoral procedures, abdominal surgery, or anticoagulation-related causes), and laboratory values before and after embolization [hemoglobin, hematocrit, platelets, and international normalized ratio (INR)]. Additional variables

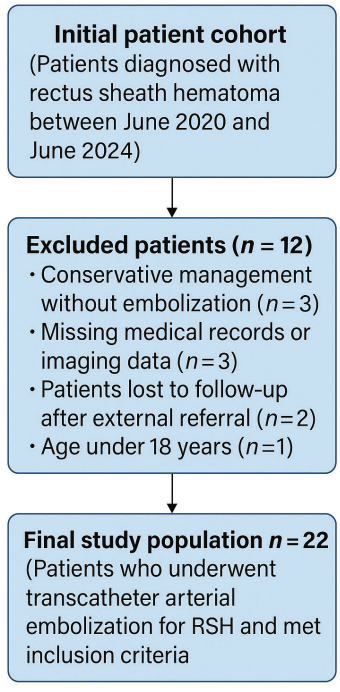

Figure 1. Flowchart of patient selection. Among 34 patients diagnosed with rectus sheath hematoma between June 2020 and June 2024, 12 patients were excluded due to conservative management, missing data, loss to follow-up, or age under 18 years. The final study population included 22 patients who underwent transcatheter arterial embolization

included the history of blood transfusion and the duration of hospital stay. Pre-embolization transfusion data were collected by counting the number of blood products administered within the 24 hours preceding embolization. Pre-embolization, hemodynamic parameters were assessed by recording the lowest hemoglobin level within this period. Similarly, post-embolization transfusion data were obtained by quantifying the number of blood products given within 24 hours after embolization, while post-embolization hemodynamic values were determined based on the lowest hemoglobin level recorded during the same timeframe.

RSH Diagnosis and Classification

The initial diagnosis of RSH was made using ultrasonography, while CT and CT angiography (CTA) provided a more detailed evaluation, enabling the assessment of retroperitoneal and extraperitoneal involvement (2,10).

Patients with RSH were classified according to the system proposed by Berná et al. (11), which categorizes hematomas based on their extent and severity.

- Type 1 RSH: Hematoma confined within the rectus muscle with minimal bleeding.
- Type 2 RSH: Hematoma extending within the rectus muscle with moderate hemorrhage.
- Type 3 RSH: Acute bleeding that extends beyond the muscle into surrounding tissues.

This classification was applied in the present study to evaluate and compare treatment outcomes among patient groups.

Angiography and TAE Procedure

Digital subtraction angiography (DSA) was performed under local anesthesia via femoral artery access on the affected side. A 5F introducer sheath was placed under ultrasound guidance, followed by catheterization of the inferior and/or superior epigastric artery using a 4F or 5F Berenstein Type 1 or 2 catheter (Cordis, Miami Lakes, FL, USA). Upon identification of a bleeding focus, selective catheterization and embolization were performed using a 2.4F coaxial microcatheter (Progreat™ Micro Catheter System; Terumo, Tokyo, Japan). Embolization was carried out using either coils (Concerto Helix Detachable Coil System, Medtronic Inc., Minneapolis, USA) or N-butyl cyanoacrylate (NBCA) (Histoacryl®, B. Braun, Tuttlingen, Germany). N-butyl cyanoacrylate embolization was performed using a mixture of NBCA and Lipiodol in a 1:6 ratio. For coil embolization, detachable coils were selected based on the diameter of the target vessel to ensure complete occlusion.

In the absence of active extravasation, empirical embolization was performed targeting the arteries supplying the hematoma site. The embolization was considered technically successful if there was complete occlusion of the target vessel(s) without residual filling on post-embolization angiography. Clinical success was determined by hemodynamic stabilization and an increase in hemoglobin levels (≥1 g/dL) within the first 24 hours following the embolization.

Statistical Analysis

All data were analyzed using SPSS Statistics Version 25.0 (SPSS, Chicago, IL, USA). The normality of numerical variables was assessed using the Kolmogorov-Smirnov test and Q-Q plots. Descriptive statistics were reported as mean ± standard deviation. Comparative statistical analyses were performed using the Mann-Whitney U test for non-normally distributed numerical variables and the Wilcoxon signed-rank test for paired data comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Etiology and Imaging Findings

A total of 22 patients (7 male and 15 female) with a mean age of 63±15.23 years met the inclusion criteria and underwent endovascular embolization in our department. The clinical and laboratory characteristics of these patients are summarized in Table 1. A sample patient is depicted in Figure 2.

Table 1. Demographics, etiology, imaging findings, embolization details of patients with rectus sheath hematoma

Patients (n)	22
Age (years)	63±15.23
Male/female ratio	7/15
Etiology of RSH n (%)	
Anticoagulation therapy Penetrating trauma Spontaneous Post-abdominal surgery Femoral endovascular procedures	11 (50%) 3 (13.6%) 3 (13.6%) 3 (13.6%) 2 (9.1%)
Laterality (Side) n (%)	
Right Left Bilateral	9 (41.9%) 11(50%) 2 (9.1%)
CT angiography findings	
Contrast extravasation Pseudoaneurysms of the inferior epigastric artery	2 (9.1%) 6 (27.2%)
Angiography findings	
Contrast extravasation Pseudoaneurysms of the inferior epigastric artery	4 (18.2%) 6 (27.2%)
Embolization material	
Coil N-butyl cyanoacrylate	18 (81.8%) 4 (18.2)
Procedure duration time (minutes) (mean+SD)	38.45±12.22
Duration of hospital stay (days) (mean+SD)	13.64±12.21

RSH: Rectus sheath hematoma, CT: Computed tomography, SD: Standard deviation

TAE Procedure and Technical Findings

The TAE procedure was performed by radiologists with at least four years of experience in vascular interventional radiology. During the procedure, pseudoaneurysms of the inferior epigastric artery were detected in 4 patients (18.2%), while active extravasation was observed in 6 patients (27.2%). In the remaining 12 patients (54.6%), no definitive bleeding focus was identified. In cases where a bleeding focus was detected, the bleeding inferior or superior epigastric artery was embolized. Technical success was achieved in 100% of cases, with complete occlusion of the target vessels confirmed on post-procedural angiography.

Transfusion Requirements and Hematologic Parameters

Prior to TAE, the mean packed red blood cell (PRBC) transfusion requirement was 2.27±2.27 units, and the fresh frozen plasma (FFP) transfusion requirement was 1.14±1.32 units. Post-embolization, these values significantly decreased to 1.09±1.15 units for PRBC (p=0.007) and 0.32±0.72 units for FFP (p=0.002), reflecting a 52% and 72% reduction in transfusion requirements, respectively.

The mean hemoglobin level increased from 8.66±2.32 g/dL pre-embolization to 10.15±2.17 g/dL post-embolization, corresponding to a 17.2% increase (p=0.004). Similarly, the mean hematocrit level rose from 26.02±6.44% to 31.4±6.34%, reflecting a 20.7% increase (p=0.001). The mean platelet count increased from 319.95±258.65×10^9/L to 370.82±287.27×10^9/L, corresponding to a 15.9% increase (p=0.023). Conversely, the INR decreased slightly from 1.51±1.02 to 1.43±0.7, but this change was not statistically significant (p=0.51) (Table 2). In two patients (9.1%), hemoglobin levels dropped within 24 hours post-embolization, requiring additional transfusion. Despite this, clinical success was achieved in 90.9% of cases with hemodynamic stabilization and hemoglobin improvement. The mean hospital stay was 13.64±12.21 days.

Procedure-Related Complications and Mortality

The procedure was well tolerated by nearly all patients, with no major complications observed. The overall complication rate was 9.1% (n=2). One patient developed a groin access site hematoma, which was managed conservatively. Another patient required additional drainage due to an infected hematoma. Both patients showed improvement during follow-up.

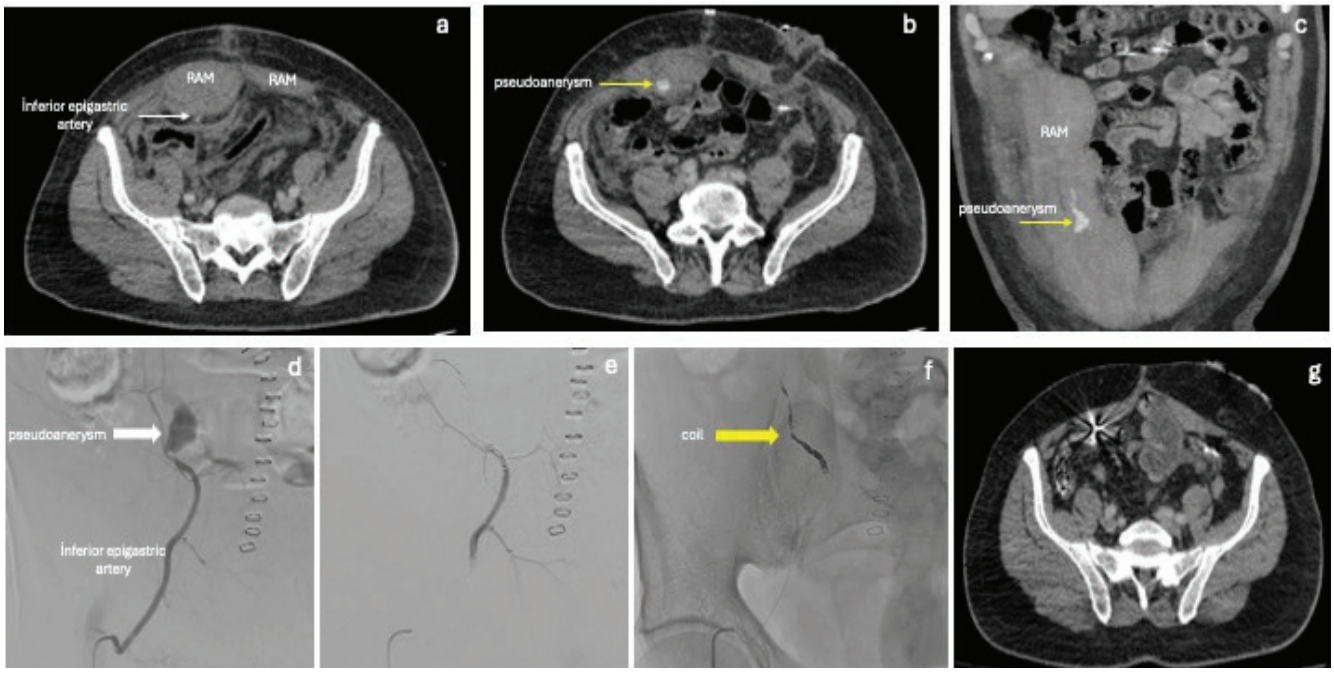

Figure 2. A 65-year-old male patient who developed right-sided RSH after surgery for colorectal cancer. **(a, b)** Axial and **(c)** coronal CT angiography images demonstrating the inferior epigastric artery (thin white arrow), a pseudoaneurysm (thin yellow arrows), and the presence of RSH, **(d)** selective angiography of the inferior epigastric artery, showing pseudoaneurysm filling (thick white arrow), **(e)** post-embolization DSA, confirming successful coil embolization with no residual pseudoaneurysm filling, **(f)** non-subtracted fluoroscopic image, displaying embolization coils (thick yellow arrow), **(g)** follow-up contrast-enhanced CT one week after the procedure, showing metallic artifact from the coils and resolution of the hematoma

RSH: Rectus sheath hematoma, RAM: Rectus abdominis muscle, DSA: Digital subtraction angiography

However, one patient (4.5%) died 17 days after the procedure due to underlying comorbidities and disease progression. This mortality was not directly related to the embolization procedure.

Hematoma Classification and Outcomes

According to the Berná et al. (11) classification, 10 patients had type 2 hematomas, while 12 patients had type 3 hematomas. The comparison of hematoma size, pre- and post-procedural transfusion requirements, hemoglobin, hematocrit, platelet count, INR levels, procedure duration, and hospital stay did not reveal any statistically significant differences among the classified groups (Table 3).

Discussion

Recognizing and appropriately managing RSH is crucial, as it is a rare but potentially life-threatening condition. While many cases can be treated conservatively, patients with hemodynamic instability or progressive hemorrhage often necessitate interventional procedures such as TAE. In recent years, TAE has emerged as a minimally invasive and effective technique for controlling RSH-related bleeding, reducing transfusion requirements, and stabilizing patients. Our study adds to the growing body of evidence by evaluating the imaging characteristics, procedural details, and clinical outcomes of patients treated with embolization over a four-year period.

Table 2. Pre- and post-embolization changes in transfusion requirements and laboratory values

Transfusion requirements and laboratory parameters	Pre-embolization	Post-embolization	Percent change (%)	p-value
Transfusions (mean+SD)				
Packed red blood cells (n)	2.27±2.27	1.09±1.15	-52	0.007
Fresh frozen plasma (n)	1.14±1.32	0.32±0.72	-72	0.002
Laboratory values				
Hemoglobin level (g/dL)	8.66±2.32	10.15±2.17	+17.2	0.004
Hematocrit level (%)	26.02±6.44	31.4±6.34	+20.7	0.001
Platelet (10^9/L)	319.95±258.65	370.82±287.27	+15.9	0.023
INR	1.51±1.02	1.43±0.7	-5.3	0.51

SD: Standard deviation, INR: International normalized ratio

Table 3. Comparison of clinical and procedural outcomes between Type 2 and Type 3 hematomas

Laboratory and clinical parameters	Type 2 hematoma n=10	Type 3 hematoma n=12	p-value
Pre-embolization (mean+SD)			
Packed red blood cells (n)	2.5±3.17	1.92±2.45	0.522
Fresh frozen plasma (n)	1.2±1.62	0.92±1.62	0.862
Hemoglobin level (g/dL)	9.02±2.27	8.66±2.32	0.391
Hematocrit level (%)	27.21±6.32	26.02±6.45	0.248
Platelet (10^9/L)	247.2±68.53	319.95±258.65	0.488
INR	1.85±1.44	1.38±0.67	0.245
Post-embolization (mean+SD)			
Packed red blood cells (n)	0.9±1.1	1.17±1.60	0.509
Fresh frozen plasma (n)	0.4±0.97	0.5±0.79	0.928
Hemoglobin level (g/dL)	10.26±2.57	10.15±2.17	0.391
Hematocrit level (%)	31.29±7.28	31.4±6.34	0.998
Platelet (10^9/L)	312.1±138.73	370.82±287.27	0.668
INR	1.85±1.44	1.51±1.02	0.143
Procedure duration time (minutes) (mean+SD)	41.5±15.01	38.45±12.22	0.129
Duration of hospital stay (days) (mean+SD)	14.6±11.98	13.64±12.21	0.321

SD: Standard deviation, INR: International normalized ratio

Notably, we observed a substantial reduction in blood product requirements following embolization, with PRBC transfusions decreasing by approximately 52% and FFP transfusions decreasing by nearly 72%. These improvements were accompanied by significant increases in hemoglobin and hematocrit levels within 24 hours, indicating rapid hemodynamic stabilization achieved through TAE in our patient cohort. Interestingly, a definitive bleeding artery could not be identified in more than half of the cases. Active contrast extravasation was detected in only 36.3% of patients on CTA and 45.5% on DSA, which is lower than the detection rates commonly reported in the literature. In the literature, the detection rate of active bleeding on CTA varies widely, ranging from 47% to 93%, while DSA has been reported to identify active bleeding in 70% to 85% of cases (7,12-14). In clinical practice, our findings emphasize that a negative CTA does not exclude ongoing bleeding, underscoring the importance of clinical evaluation in determining the need for embolization. In cases without visible extravasation, we frequently performed empirical embolization of the epigastric arteries, which proved to be a highly effective strategy. Recent evidence supports this approach, with a 2024 meta-analysis showing no significant difference in rebleeding rates between empirical and targeted TAE techniques (3).

Rectus sheath hematoma can be life-threatening, especially in vulnerable patients, with recent series reporting early mortality rates of 24-30% despite intervention (4). In this context, our findings demonstrate that prompt TAE provides highly effective hemorrhage control in RSH. In this study, we achieved a 100% technical success rate and a 90.9% clinical success rate, with no hemorrhage-related deaths. These results are consistent with existing literature, where reported technical success rates range from 96% to 100%, and clinical success rates vary between 65% and 93% (1,12-14). The high success rate observed in our study underscores the critical role of TAE in the management of severe RSH and aligns with the positive outcomes reported in contemporary series of spontaneous soft-tissue hemorrhages. However, the variability in clinical success criteria across studies complicates direct comparisons, highlighting the need for standardized definitions to improve consistency in future research.

The selection of embolic agents in RSH management is primarily guided by angiographic findings and operator experience. Coils are often preferred due to their controlled deployment and lower risk of non-target embolization, particularly when selective catheterization of the bleeding vessel is feasible. Conversely, in cases with diffuse or poorly accessible bleeding, NBCA provides the advantage of rapid and effective vascular occlusion. In our series, both coils and NBCA were used successfully, with no procedure-related complications observed for either material (15). These findings align with recent studies demonstrating the efficacy and safety of NBCA in emergency embolization scenarios. For instance, a large 2025 series evaluating 113 acute hemorrhage cases reported an 82% clinical success rate with NBCA, without major complications, underscoring its value as a reliable embolic agent when applied judiciously (5). Thus, while coils remain the preferred choice in selective embolization, liquid agents like NBCA are indispensable in complex bleeding patterns, offering complementary strategies for achieving hemostasis.

Berná et al. (11) proposed a diagnostic classification for RSH based on CT findings. Type 1 hematomas are mild and do not require hospitalization, while Type 2 hematomas are moderate and necessitate hospitalization. Type 3 hematomas are more severe, typically occurring in patients on anticoagulant therapy and often requiring blood transfusion (16). In the literature, there is no study comparing the endovascular treatment outcomes of Type 2 and Type 3 hematomas. In this study, we found no significant differences in laboratory value changes or blood product requirements between patients with Type 2 and Type 3 RSH who underwent endovascular treatment.

Study Limitations

Several limitations of this study should be acknowledged. Our findings, based on a retrospective single-center analysis, suggest that our findings may not be generalizable to broader populations. Additionally, we did not compare embolization outcomes with alternative management strategies, such as conservative treatment or surgical intervention, which limits our ability to draw definitive conclusions regarding the superiority of TAE. Another limitation is the relatively small sample size, which may reduce the statistical power of our analysis, particularly in subgroup comparisons. Furthermore, long-term follow-up data on recurrence rates were not available, which could have provided additional insights into the durability of TAE outcomes. Despite these limitations, this study has notable strengths. It represents a consecutive series of patients treated in a high-volume tertiary center, ensuring a standardized treatment protocol and homogeneous patient management. The study provides detailed procedural data, including embolization techniques and materials, and offers valuable insights into the effectiveness of TAE in a real-world clinical setting. Furthermore, the systematic evaluation of pre- and post-procedural hematologic parameters strengthens the reliability of the clinical outcomes reported.

Conclusion

This study demonstrates that TAE is an effective and safe treatment modality for RSH. Particularly in patients with hemodynamic instability or those unresponsive to conservative management, TAE reduces transfusion requirements and contributes to clinical stabilization. Our findings support the consideration of TAE as an important therapeutic option within the management algorithms of RSH.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained from the Basaksehir Cam and Sakura City Hospital Ethics Committee (approval no.: 130, date: 24.07.2024).

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.E., T.G., M.C., A.D., M.F.A., O.T., Concept: C.E., T.G., M.H.T., M.C., M.F.A., I.N.M., N.O.K., Design: C.E., M.H.T., A.D., O.T., I.N.M., N.O.K., Data Collection or Processing: C.E., Z.O., M.C., MF.A., Analysis or Interpretation: C.E., T.G., Z.O., M.C., A.D., M.F.A., I.N.M., N.O.K., Literature Search: C.E., Z.O., M.H.T., A.D., O.T., I.N.M., N.O.K., Writing: C.E., T.G., M.H.T, O.T.

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Case Report

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An Elusive Diagnosis: Primary Breast Angiosarcoma with Metastatic Spread-A Case Report and Literature Review

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Abstract

Breast angiosarcoma is an extremely rare disease that is more aggressive than mammary carcinomas. A 38-year-old woman was admitted to the hospital with breast edema. Mastitis was suspected, and biopsies were done, but no cancer was found. Her follow-up revealed a lesion with axillary involvement. She underwent neoadjuvant chemotherapy. Her mastectomy was scheduled when lung metastases were found during treatment. The pathology report indicated high-grade angiosarcoma. She underwent adjuvant chemotherapy. Brain metastases were identified, and she died during her follow-up. Radiological imaging may potentially miss it or misidentify it as a benign lesion. The literature has identified several treatment approaches, but due to the small number of patients, no specific guidelines exist. This case demonstrated that the disease is challenging to diagnose, and that magnetic resonance imaging can serve as an effective diagnostic instrument.

Keywords: Breast cancer, breast, primary breast angiosarcoma, metastasis

Introduction

Angiosarcomas, which are uncommon breast tumors of soft tissue, can manifest in both primary and secondary forms. The primary form lacks a known precursor, while the secondary form records radiation exposure to the breast tissue. Primary mammary angiosarcomas are aggressive tumors with a high propensity for local recurrence and distant metastasis, as well as a high risk of mortality due to the tumor (1,2).

This article presents a 38-year-old patient with metastatic high-grade angiosarcoma in the right breast. She underwent a mastectomy and had pulmonary metastases prior to and after the procedure. She later developed brain metastases and lesions on her tongue, identified as lobular capillary hemangiomas. She died of her disease.

Case Report

Our case represents a patient with metastatic primary breast angiosarcoma (BA) and all necessary informed consents were obtained from the patient prior to the operation. In 2019, a 38-year-old female patient presented with right breast edema and pain at a rural hospital. The ultrasound of the breast indicated a nodule and mastitis. A trucut biopsy reveals no cancer in this tumor. A 5 cm lesion and purulent discharge on her right breast led to her hospitalization one month later. The prior biopsy raised suspicion of granulomatous mastitis; however, no granuloma was detected, and malignancy could not be excluded.

She received a mammography as part of her routine national breast screening program follow-ups, which identified a BIRADS-4 lesion. Following this, she

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***This case was presented as a poster presentation in the 23rd Turkish National Surgical Congress at Antalya (April 2024) and the abstract was added to the congress book.**

conducted a biopsy on the lesion, leading to the diagnosis of an angiosarcoma. The positron emission tomography/computed tomography (CT) scan identified a 70x63 mm tumor in her right breast with increased fluorodeoxyglucose (FDG) uptake (SUV_{max}=8.2), along with right axillary lymph nodes at level 1, the largest of which measured 14 mm in diameter and showed increased FDG uptake (SUV_{max}=3).

She attended our hospital's oncology clinic and received paclitaxel as neoadjuvant chemotherapy. A CT scan of the chest and abdomen was performed following three cycles of therapy. Several metastatic lesions in her lungs, the largest measuring 8 mm were identified.

Immediately after the discovery of her lung metastases, the oncology clinical meeting reviewed the case and scheduled a mastectomy. The final pathology indicated a high-grade angiosarcoma with significant vascular cavity invasion. Eight lymph nodes were identified as reactive. The immunohistochemistry examination demonstrated widespread endothelial staining with CD31, CD34, and factor 8. Mammoglobin, GCDFP15, and HHV8 are negative. Her Ki-67 index is 70-75%. The lesion measures 7x5x3.5 cm (American Joint Commitee on Cancer-pT3N0M1). The tumor displays significant hemorrhagic regions, fibrin accumulation, and necrosis, alongside endothelial arrangement around the vascular space, solid cellular proliferation, endothelial cell budding, papillary formations, mild atypia, nucleoli, and mitotic activity. The vascular space is extensively invaded. No tumor is present in the sections of breast skin, nipple, or areola. The tumor extends 0.2 cm from the operative margin of the fascia (Figures 1-4).

On postoperative day 13, CT scans of the thorax demonstrated numerous nodules in both lungs, some exhibiting contrast enhancement. The patient is then assigned an *ifosfamide, mesna, adriamycin*-IMA chemotherapy regimen for palliative treatment. A control thoracic CT was conducted on her after three months and three cycles. Her CT images demonstrated several metastatic nodules, the largest measuring 6 millimeters in diameter. The quantity, dimensions, and density of the nodules markedly diminished in comparison to the patient's prior thoracic CT scan.

Following the conclusion of the fourth cycle, an magnetic resonance imaging (MRI) of her brain indicated no signs of metastases. She then finished three more cycles, resulting in a total of six therapy cycles. After completing her chemotherapy program, she developed brain metastases and lesions on her tongue, later diagnosed as lobular capillary hemangiomas. She subsequently died from her illness.

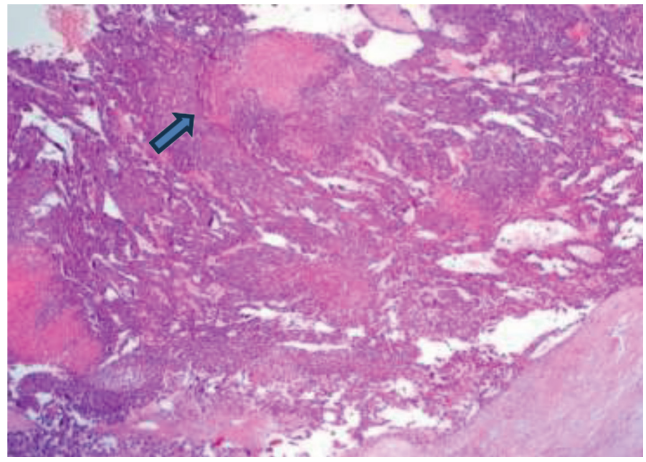

Figure 1. The tumor consists of papillary structures and vascular formations, with areas of necrosis observed (x40)

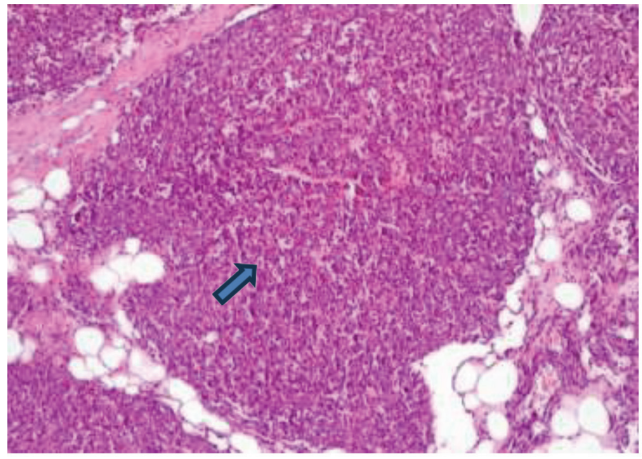

Figure 2. Solid areas with spindle cell morphology and limited vascular structures are observed (x100)

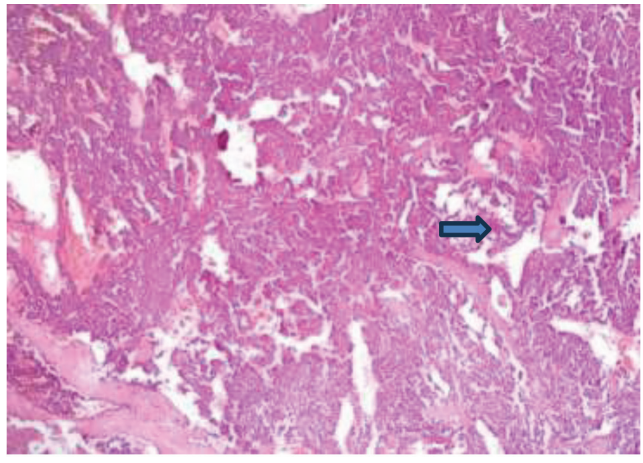

Figure 3. Extensive hemorrhagic areas are present between the papillary formations (x40)

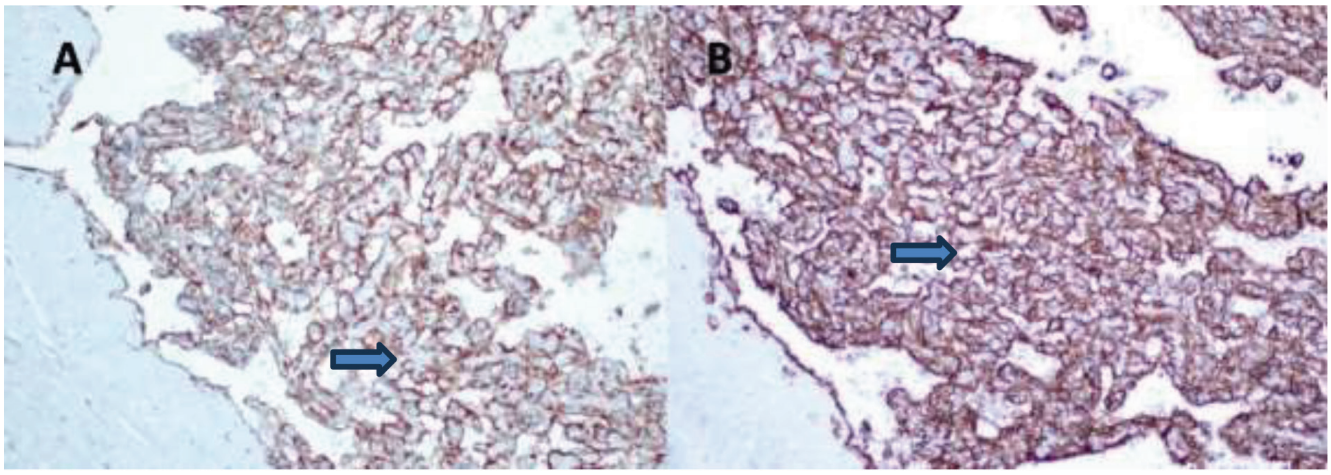

Figure 4. In the immunohistochemical study, tumor cells show diffuse positivity with CD31 (Panel A) and CD34 (Panel B) (x200)

Discussion

Breast cancer is the most common type of cancer and the leading cause of mortality among women worldwide (3-6). The World Health Organization classification categorizes invasive breast cancer into 21 unique histological categories based on cellular shape, growth characteristics, and structural patterns (7). Breast angiosarcoma is an extremely rare disease with an incidence rate of less than 0.05% of all breast cancers (2).

The appearance of BA's on mammograms is non-specific. Young women's high breast density can easily obscure findings such as focal asymmetry or an ill-defined non-calcified lesion (8,9). Yang et al. (10) analyzed BA patients and found that 1,9% of angiosarcomas are not visible on mammograms but are detectable with ultrasound imaging. Kaklamanos et al. (11) also pointed out that imaging methods like mammography and ultrasound can misdiagnose these lesions as benign since they don't show the typical signs of adenocarcinoma, especially in younger women. Breast MRI is frequently useful for detecting these types of lesions (11).

Sebastian et al. (12) revealed that the lesions may be overlooked in imaging studies. Despite their patients undergoing wide local excision, they recommended mastectomy as the primary treatment choice. Magnetic resonance imaging should be the primary modality, and vascular markers like CD31 and CD34 can assist in pathological diagnosis. In our case, we also used these markers for diagnosis (12).

Borrman (13) reported the first case in 1907, and due to the rarity of these cases, therapeutic recommendations and prognostic factors are not well-established. According to several studies, the surgery of choice for the majority of patients with angiosarcomas and primary breast sarcomas is total mastectomy, or in some cases, total mastectomy and axillary dissection. Kaklamanos et al. (11) suggested that smaller lesions could potentially benefit from breast-conserving surgery as a treatment option. There are also articles suggesting that axillary dissection is unnecessary because angiosarcomas metastasize via the vascular system.

Iacoponi et al. (14) reported performing a nipple-sparing mastectomy and breast reconstruction on a patient with a grade 1 angiosarcoma that completely occupied the right breast, followed by adjuvant chemoradiotherapy. They indicate that the patient is asymptomatic and disease-free thirteen months after the primary diagnosis.

Killoran and Dissanayake (15) reported a case of a 79-year-old woman diagnosed with primary BA. The patient had wide local excision, removal of muscle and fascia, and reconstruction of the chest wall using the latissimus dorsi flap. During her follow-up, the patient developed lung metastases and received palliative chemotherapy similar to our patient. They indicated that the impact of neoadjuvant treatment on the prognosis is unknown. They also observed that early MRI assists in the diagnosis (15).

Vohra et al. (16) documented a case of an 87-year-old patient diagnosed with primary angiosarcoma, with no metastases at the initial assessment. She underwent a mastectomy. They utilized CD34 markers to validate the final pathology specimen, similar to our approach. After a follow-up regimen of three months, the patient experienced widespread metastases, which ultimately led to her death from the disease. They recommended complete mastectomy as the surgical procedure and advised against axillary surgery unless axillary disease is confirmed (16).

Due to the small number of known patients with primary BA, there are no studies examining the effects

of adjuvant chemotherapy or radiotherapy. Some retrospective studies suggest that patients at high risk for recurrence (tumors of high grade and size) may benefit from adjuvant therapy. According to some authors, this tumor may be chemosensitive, and the administration of chemotherapy for specific patients can increase survival (11).

Our patient was a 38-year-old woman who presented to the hospital with right breast pain and swelling. The inability to make a definitive diagnosis in a rural hospital may be due to the absence of an MRI. This is because this type of tumor often does not display its characteristic features on mammograms and ultrasounds, especially in young women. She received neoadjuvant chemotherapy, during which she developed pulmonary metastases. Then she had a salvage mastectomy. The metastasis in her lungs regressed after the addition of palliative chemotherapy to her treatment plan. But finally, she developed brain metastasis and died of her condition. Due to the limited number of patients with primary BA, there is no specific guideline for determining surgery and adjuvant/neoadjuvant treatment plans.

Conclusion

This case demonstrated that the disease is challenging to diagnose and that MRI can serve as an effective diagnostic instrument. Our case demonstrated that, despite undergoing a salvage mastectomy and supplementary palliative care, a patient with lung metastases can experience disease progression. By analyzing our patient and the limited cases documented in the literature, clinicians can formulate a treatment strategy. Further research is necessary to establish particular guidelines for this kind of breast cancer.

Ethics

Informed Consent: All necessary informed consents were obtained from the participants

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.B.A., K.C., S.K., A.Y., Concept: M.B.A., K.C., Design: M.B.A., K.C., Data Collection or Processing: M.B.A., K.C., S.K., Analysis or Interpretation: M.B.A., K.C., Literature Search: M.B.A., K.C., Writing: M.B.A., K.C., S.K., A.Y.

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