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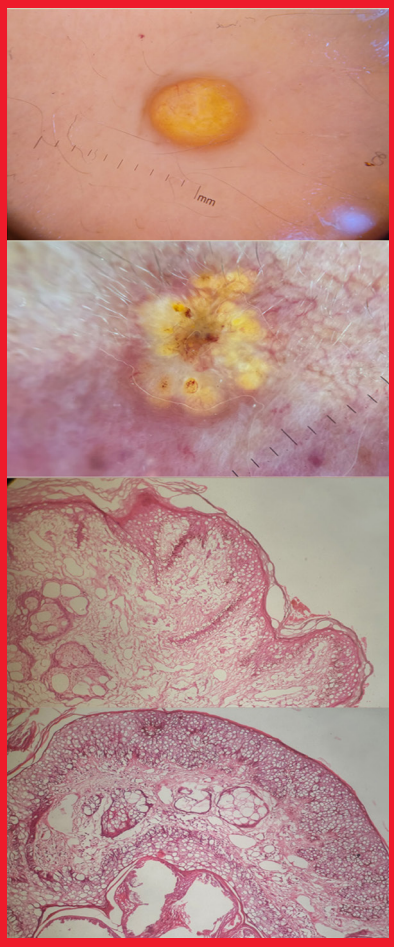

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr

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EDITORIAL

Dear Readers;

We are pleased to share the April 2026 issue of Bezmialem Science with you. Our journal, which aims to bring together high-quality research conducted in various fields of health sciences, continues to feature studies that emphasize the interdisciplinary power of scientific production in this issue as well. Inspired by the long-standing foundation tradition of Bezmialem Vakıf University, we are proud to continue our publishing approach that integrates science with a human-centered approach and ethical values.

The cover image for this issue is selected from the study entitled "Nevus Sebaceus of Jadassohn: A Clinicopathological and Dermoscopic Study with Management Implications" by Kaya G, Özgün Geçer M, Alavanda C, and Yabacı Tak A. This original study aims to comprehensively evaluate the clinical, dermoscopic, and histopathological features of Jadassohn's Nevus Sebaceus. In a patient series encompassing different age groups, stage-dependent morphological changes in lesions were demonstrated, showing that yellowish globules were associated with early stages, while gray papilliform structures were associated with advanced stages. No malignancy was detected in this study, and it is emphasized that dermoscopy, as a non-invasive method, provides important clues for diagnosis and monitoring. The findings suggest that a conservative approach may be appropriate in low-risk cases, while surgical excision should be considered in advanced-stage or clinically suspicious lesions, providing guidance for clinical management.

Other articles featured in this issue include:

"Course of Patients with Pneumonia Hospitalized After Outpatient Treatment: A Two-year Single-center Experience" by Nalbant E and Genç F.

"The Effects of Delivery Room Admission Time on the Labor Process, Neonatal Outcomes, and Women's Traumatic Birth Perceptions: A Comparative Study" by Öztaş HG and Filiz A.

"The Diagnostic Value of Combined Hip and Systemic Ultrasonography for the Early Detection of Developmental Dysplasia of the Hip and Associated Pathologies in Infants" by Gönen KA et al.

"Who is More Aggressive in the Race to Diagnose Pulmonary Embolism? General Practitioners or Emergency Medicine Specialists: A Multicenter Study" by Kanter E et al.

We believe that it is of great importance not only to produce scientific knowledge, but also to transform it into healthcare services, clinical applications, and societal benefit. In this regard, we take care to ensure that the studies we publish in our journal are methodologically strong, innovative, and contribute to practical application. The diverse perspectives and interdisciplinary collaborations of our researchers make significant contributions to accelerating developments in the field of health sciences.

I would like to express my gratitude to all the authors who contributed to the preparation of this issue, to our editors who meticulously evaluated the articles, and to our valuable reviewers. Their dedicated contributions to improving scientific quality play a significant role in the development of our journal.

I hope that the April 2026 issue will be useful and inspiring for all researchers and clinicians working in the field of health sciences, and I would like to state that as the Bezmialem Science family, we will continue to contribute to scientific production.

Sincerely,

Prof. Dr. Adem AKÇAKAYA
Editor-in-Chief

Original Article

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Bezmialem Science 2026;14(2):106-111

Course of Patients with Pneumonia Hospitalized After Outpatient Treatment: A Two-year Single-center Experience

Ayaktan Tedavi Sonrası Hastaneye Yatırılan Pnömoni Hastalarının Seyri: İki Yıllık Tek Merkez Deneyimi

Ercan NALBANT, Fatih GENÇ

University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital, Department of Emergency Medicine, Trabzon, Türkiye

ABSTRACT

Objective: This study evaluated the demographic characteristics of patients treated for lower respiratory tract infections. We also examined patients who were initially hospitalized and those who received outpatient treatment before being hospitalized. We investigated the effects of CURB-65 scores at presentation or at the time of transfer to intensive care unit (ICU), use of invasive or non-invasive oxygen supplementation, comorbidities, and repeated hospital admissions.

Methods: This single-center, retrospective study was conducted at the Emergency Department of University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital. Using hospital automation records, we analyzed pneumonia cases admitted and hospitalized between January 1, 2022, and December 31, 2023. The study included non-pregnant adult patients aged 18 and older, based on specific inclusion and exclusion criteria.

Results: A total of 625 patients were included. Of these, 27.8% were hospitalized after a second admission. No significant differences were found between first and second admission groups in terms of age, gender, comorbidities, CURB-65 scores, ICU requirement, or invasive ventilation ($p>0.05$). However, mortality was significantly higher among patients who required intubation ($p<0.01$). There was no significant association between the number of admissions and mortality ($p=0.784$).

Conclusion: The number of hospital admissions was not found to be a primary predictor of mortality in patients with

ÖZ

Amaç: Bu çalışmada, alt solunum yolu enfeksiyonu nedeniyle tedavi edilen hastaların demografik özellikleri değerlendirildi. Ayrıca, ilk başvuruda hastaneye yatırılan ve öncesinde ayaktan tedavi alıp hastaneye yatırılan hastalar incelendi. Hastaların başvuru anındaki veya yoğun bakıma transfer anındaki CURB-65 skorları, invaziv ya da non-invaziv oksijen desteği kullanımı, eşlik eden hastalıkları ve tekrarlayan hastane başvurularının etkisi araştırıldı.

Yöntemler: Bu tek merkezli, retrospektif çalışma Sağlık Bilimleri Üniversitesi, Trabzon Kanuni Eğitim ve Araştırma Hastanesi Acil Servisi'nde yürütüldü. 1 Ocak 2022 ile 31 Aralık 2023 tarihleri arasında acil servise başvurarak hastaneye yatırılan pnömoni olguları, hastane otomasyon sistemi kullanılarak analiz edildi. Çalışmaya, belirlenen dahil etme ve dışlama kriterlerine göre seçilen, 18 yaş ve üzerindeki gebe olmayan erişkin hastalar dahil edildi.

Bulgular: Toplam 625 hasta çalışmaya alındı. Bu hastaların %27,8'i ikinci başvurularında hastaneye yatırılmıştı. İlk ve ikinci başvuru grupları karşılaştırıldığında; yaş, cinsiyet, eşlik eden hastalıklar, CURB-65 skorları, yoğun bakım ihtiyacı ve invaziv ventilasyon gereksinimi açısından anlamlı fark saptanmadı ($p>0,05$). Ancak, entübasyon gerektiren hastalarda mortalite anlamlı olarak daha yüksekti ($p<0,01$). Başvuru sayısı ile mortalite arasında anlamlı bir ilişki bulunmadı ($p=0,784$).

Sonuç: Pnömoni hastalarında hastane başvuru sayısı mortalite için birincil belirleyici değildir. Sadece invaziv mekanik ventilasyon ihtiyacı ile mortalite arasında anlamlı bir ilişki bulunmuştur. Bu bulgular, pnömoni yönetiminde ve

Address for Correspondence: Ercan Nalbant MD, University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital, Department of Emergency Medicine, Trabzon, Türkiye
E-mail: dr.nalbant.ercan@gmail.com
ORCID IDs of the authors: E.N.: 0000-0002-5470-4519, F.G.: 0009-0004-5128-3001

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ABSTRACT

pneumonia. Only the need for invasive mechanical ventilation showed a significant association with mortality. These findings indicate that clinical severity, rather than readmission frequency, may be more critical in determining outcomes in pneumonia management.

Keywords: Community-acquired pneumonia, CURB-65, readmission

ÖZ

prognozunda tekrar başvuru sayısından ziyade klinik şiddetin daha belirleyici olduğunu göstermektedir.

Anahtar Kelimeler: Toplum kökenli pnömoni, CURB-65, tekrar başvuru

Introduction

Although community-acquired pneumonia (CAP) is one of the most frequently encountered infectious diseases universally, it is a very serious global health problem in terms of mortality and morbidity (1). "Typical'' cases of CAP usually present with classical symptoms such as fever, productive cough, dyspnea and pleuretic ribcage pain, while "atypical'' CAP is characterized by subacute onset, diffuse lung infiltration and extrapulmonary symptoms (1). Symptoms and clinical findings are not sufficient to reliably differentiate the exact etiologic agent (2).

Prognostic factors associated with unfavorable clinical course in CAP include cardiovascular diseases, chronic liver disease, splenic dysfunction, advanced age, multiple lobar lung involvement, history of previous tuberculosis disease and delayed treatment approaches (3). Since the 19th century, many evaluations have been made about the disease in terms of different clinical presentations and its effects on immunocompromised elderly individuals (4).

A meta-analysis published in 2024 examined the risk factors affecting mortality in patients with severe pneumonia. According to the results of the study, male gender and advanced age, malignancy, septic shock and renal failure were among the factors that significantly affected mortality (5). Secondary bacterial pneumonia also causes an increase in the risk of mortality, but patients over 65 years of age and in need of mechanical ventilation are in the risky group (6).

Various scoring systems have been developed to assess the severity of CAP and to determine the treatment strategy. Pneumonia severity index (PSI) and CURB-65 are the main scoring systems used. In CURB-65 scoring, the patient's state of consciousness, urea level in the blood, respiratory rate per minute, blood pressure and age are used (Table 1) (7). A score of 0-1 indicates a low risk of death (1.5%) and requires outpatient treatment, a score of 2 indicates a moderate risk of death (9.2%) and requires hospitalization, a score of 3 indicates a high risk of death (22%) and requires hospitalization, and a score of 4-5 indicates a very high risk of death and requires intensive care unit (ICU) follow-up (8). Patients who need mechanical ventilation are in the risky group (6).

A cohort study in Colombia evaluated the use of 16 different risk scores in predicting mortality at 3, 6, and 12 months; the PSI, CRB-65, and CURB-65 scores were found to be effective in predicting short-term mortality but limited in long-term prediction (9). Other studies also showed that the PSI and CURB-65, although limited in accuracy, were effective in predicting 30-day mortality (10). In a study of emergency departments, the CURB-65 score predicted mortality risk for patients scoring 1 or more points with 38% specificity and 92.8% sensitivity (11). A study in Iran reported that the CURB-65 score was similarly accurate to the PSI scores, but the CURB-65 score was more easily applicable (12).

With an ageing population and increasing burden of comorbidities, hospital admissions for CAP are expected to increase. In addition to individual health problems, this has serious implications for resource management in the health system. Although currently used scoring systems are effective in early mortality risk prediction, they have limited predictive power in terms of recurrent hospital admissions and long-term outcomes. When we look at the literature, comprehensive studies on the demographic characteristics, clinical course and mortality of patients with recurrent hospital admissions due to lower respiratory tract infection are very limited. This study aims to fill this knowledge gap from a different perspective and aims to contribute to making patient treatment strategies more effective by examining the demographic characteristics, differences in treatment processes and mortality rates of this patient group hospitalized with readmission.

Methods

Our study was conducted in the adult emergency department, and the cases admitted to the emergency department and diagnosed with pneumonia were retrospectively screened. Approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Trabzon Kanuni Training and

Table 1. CURB-65 scoring system

	Definition
Unconsciousness, confusion	Yes=1 point or No=0 point
Urea (blood urea nitrogen)	>19 mg/dL=1 point
Respiration rate	>30 /min=1 point
Blood pressure	Systolic <90 mmHg or diastolic <60 mmHg=1 point
Age	Age ≥65=1 point

Research Hospital (decision no: 2024/97, date: 26.06.2024). Patients admitted to the emergency department and hospitalized in a retrospective 24-month period were included in the study. Patients under 18 years of age, patients who refused treatment, and patients with missing data in their files were excluded from the study as part of the exclusion criteria. Necessary laboratory and imaging tests, vital signs, demographic data, and the course of treatment during hospitalization were obtained from the hospital automation system.

Statistical Analysis

All data were recorded in Microsoft Excel file and evaluated. Analyses were performed using Jamovi v.1.6 statistical software [The Jamovi Project (2021)] Computer Software, version 1.6. Sydney, Australia). Categorical data were expressed as frequency (n) and percentage. Normally distributed continuous data were expressed as mean plus standard deviation and non-normally distributed data were expressed as median and interquartile range (IQR). Normality of distributions was evaluated by Shapiro-Wilk test. Student's t-test was used to compare continuous variables in the presence of normal distribution and Mann-Whitney U test was used in the absence of normal distribution. Chi-square test was used to compare categorical variables between groups.

Table 2. The patients' demographic data and baseline characteristics

Characteristics	All patients (n=625)
Gender	
Male, n (%)	340 (54.4%)
Female, n (%)	285 (45.6%)
Age (years), median (IQR)	77 (IQR: 67-84)
Hospital admission	
First admission	451 (72.2%)
Median age	78 (IQR: 68-85)
Second admission	174 (27.8%)
Median age	74 (IQR: 66.5-83)

IQR: Interquartile range (25^{th}-75^{th} percentile)

Results

A total of 625 patients who presented to the emergency department with complaints of lower respiratory tract infection and were diagnosed with pneumonia and hospitalized between January 1, 2022, and December 31, 2023, were examined. Of the 625 patients hospitalized with a diagnosis of pneumonia, 340 (54.4%) were male and 285 (45.6%) were female (Table 2). The median age of all patients was determined to be 77 years (IQR: 67-84). One hundred seventy-four (27.8%) of the patients had previously received treatment and were hospitalized after a second hospital admission. The median time to readmission for patients admitted on a second admission was calculated as 3 days (IQR: 2-5). The median age of 451 patients hospitalized on their first visit was 78 (IQR: 68-85), and the median age of 174 patients hospitalized on their second visit was 74 (IQR: 66.5-83) (Table 2).

When the ages of patients hospitalized on repeat visits after outpatient treatment were compared with those of patients hospitalized on their first visit, no statistically significant difference was found between the groups (p=0.071) (Table 3).

Of the patients who were hospitalized at the readmission, 99 were male and 75 were female. In the comparison by gender, no statistical difference was observed in terms of hospitalization rates at repeat admission (p=0.491). When the CURB-65 scores of all patients calculated at the time of admission were analyzed, it was observed that 280 (44.8%) patients were most frequently evaluated with a score of 2, followed by 137 (21.9%) patients with a score of 1. Other score distributions were observed at decreasing rates (Table 4). The median CURB-65 score of the entire patient group at admission was 2 (IQR: 1-2).

Of the 451 patients hospitalized at their first presentation, 209 (46.3%) and 71 (40.8%) of the 174 patients hospitalized

Table 3. Statistical analysis of the first and second hospital admissions

Characteristics	All patients (n=625)	First admission	Second admission	p-value
Gender				
Male, n (%)	340 (54.4%)	241 (70.8%)	99 (29.2%)	0.491^
Female, n (%)	285 (45.6%)	210 (73.7 %)	75 (26.3%)	
Age (years), median (IQR)	77 (IQR: 67-84)	78 (IQR: 68-85)	74 (IQR: 66.5-83)	0.071*
CURB-65	2 (IQR: 1-2)	2 (IQR: 1-2)	2 (IQR: 1-2)	0.128*
Ward admission	397 (63.5%)	293 (73.8%)	104 (26.2%)	0.264^
Intensive care unit admission	228 (36.5%)	158 (69.3%)	70 (30.7%)	
Invasive oxygenation	151 (24.2%)	109 (72.2%)	42 (27.8%)	1.000^
Non-invasive oxygenation	474 (75.8%)	342 (72.2%)	132 (27.8%)	
Death	180 (28.8%)	128 (28.4%)	52 (29.7%)	0.784^

IQR: Interquartile range (25^{th}-75^{th} percentile), *: Mann-Whitney U test, ^: x^2 test

at their second presentation had a CURB-65 score of 2. No statistically significant difference was found between the groups in terms of CURB-65 score distribution (p=0.128) (Table 3). However, when the mortality group and the recovery discharged patient groups were compared, a significant difference was found between the mean CURB-65 values (p<0.001). Of the patients, 246 had diagnosed lung disease, and 173 (70.3%) were hospitalized at their first presentation. Eighty-eight patients had a history of malignancy, and 66 (75%) were hospitalized at their first presentation. One hundred fifty eight (70.8%) of the 223 patients with congestive heart failure (CHF), 154 (77%) of 200 patients with a prior diagnosis of cerebrovascular disease (CVD), 102 (76.6%) of 133 patients with chronic kidney disease (CKD), and 17 (80.9%) of 21 patients with liver disease were initially hospitalized. Additionally, 225 patients had diabetes mellitus (DM) and 401 patients had hypertension (HT), and 159 (70.6%) and 296 (73.8%) of these patients were initially hospitalized, respectively.

When comorbid diseases were analyzed, no statistically significant difference was found between the need for hospitalization at the first and second admissions in terms of DM (p=0.591), HT (p=0.141), chronic lung disease (p=0.465), malignancy (p=0.382), CHF (p=0.746), CVD (p=0.054), CKD (p=0.170) and liver disease (p=0.181) (Table 5).

A total of 228 patients (36.5%) required follow-up in the ICU during hospitalization, with a median length of stay of 7 days (IQR: 3-14.5). Treatment in ICU was needed in 158 (69.3%) of the patients hospitalized at the first admission and 70 (30.7%) of the patients hospitalized at the second admission. There was no significant correlation between the number of admissions and follow-up in ICU (p=0.264) (Table 3).

Table 4. Frequencies of CURB-65

Levels	Counts	% of total	Cumulative %
0	56	9	9
1	137	21.9	30.9
2	280	44.8	75.7
3	57	9.1	84.8
4	59	9.4	94.2
5	36	5.8	100

One hundred fifty one (24.2%) patients required invasive mechanical ventilation support during the treatment process. When the need for intubation was analyzed according to the number of admissions, 109 (72.2%) of the patients hospitalized at the first admission and 42 (27.8%) of the patients hospitalized at the second admission were intubated. There was no statistically significant relationship between the number of admissions and the need for invasive ventilation (p=1.000).

During the treatment, 137 (90.7%) of the patients who needed intubation and 43 (9.3%) of the patients who did not need this support died. When the relationship between the need for intubation and mortality was analyzed, a correlation was found between intubation and mortality (p<0.01). This suggests that the need for invasive oxygenation may be an indicator of poor prognosis. One hundred eighty (28.8%) hospitalized patients died. Of these patients, 128 (71%) were hospitalized at the first admission and 52 (29%) were hospitalized at the second admission. When the mortality rates of the patients were compared with the number of admissions, no statistical significance was found between the number of admissions and mortality (p=0.784) (Table 3).

Discussion

A meta-analysis of 101 different studies analyzing data on approximately 17 million hospitalizations in the United States revealed that advanced age was a significant parameter in hospital admissions and in-hospital mortality. In developed countries, hospitalization rates due to pneumonia were recorded as 17.3/1.000 in men and 12.9/1.000 in women, while in-hospital mortality rates were reported as 11.6-11.9% in men and 9.8-10.2% in women (13). In contrast, in our study, no statistical difference was observed in terms of age (p=0.071) and gender (p=0.491) distributions between patients who were hospitalized at initial admission and who were hospitalized at recurrent admission.

According to our study, comorbidities did not make a difference between the rates of hospitalization at initial and repeated admissions in patients with pneumonia; however,

Table 5. Statistical analysis of hospital admission rates at first and second hospital presentations according to comorbidities

Comorbidity	Number of patients	First admission	Second admission	p-value*
Pulmonary disease	246 (39.4%)	173 (70.3%)	73 (29.7%)	0.465
Malignancy	88 (14.1%)	66 (75%)	22 (25%)	0.382
Congestive heart failure	223 (35.7%)	158 (70.8%)	65 (29.2%)	0.746
Cerebrovascular disease	200 (32%)	154 (77%)	46 (23%)	0.054
Chronic kidney disease	133 (21.3%)	102 (76.6%)	31 (23.4%)	0.170
Hepatic disease	21 (3.4%)	17 (80.9%)	4 (19.1%)	0.181
Diabetes mellitus	225 (36%)	159 (70.6%)	66 (29.4%)	0.591
Hypertension	401 (64.4%)	296 (73.8%)	105 (26.2%)	0.141
*: x^2 test				

it has been reported in the literature that malignancy, CHF, CKD, DM with complications and dementia have negative effects on mortality (14). Especially the fact that malignancy and CKD have a strong correlation with mortality suggests that comorbidities affect patient prognosis rather than hospitalization decisions.

In a retrospective study conducted on the CURB-65 score, patients were scored from 0 to 4 and 52.31% of the patients were scored 3 points and 35.38% were scored 2 points during hospitalization. In terms of mortality, a significant increase in mortality was observed as the score obtained from the scoring increased, and the patient group with a score of 4 had the highest mortality with a mortality rate of 33.33% (15). In our current study, the median CURB-65 score of the patients hospitalized in both the first and second admissions was 2 (IQR: 1-2). As expected, a significant difference was found between the discharged patients and pneumonia-related deaths in terms of score ($p<0.001$). This result suggests that the CURB-65 score is a reliable marker of pneumonia prognosis.

In the literature, it is emphasized that patients with a CURB-65 score of 2 or above should be treated as inpatients and patients with a score of 3 or above should be evaluated for ICU hospitalization (16). In our study, the fact that the group of patients who presented for the second time and received inpatient treatment consisted of individuals who were followed up as outpatients after the first presentation and presented again was important especially in terms of observing the critical deterioration period after discharge. When the initial and repeat presentations were compared in terms of the need for ward and ICU hospitalization, no significant difference was found ($p=0.264$).

A study conducted during the coronavirus disease 2019 pandemic reported that of 56,715 suspected cases, 20.7% were hospitalized, 2.9% were intubated, and the total mortality rate was 8.1% (17). Our findings were consistent with these data, and while there was no statistical difference between the need for invasive mechanical ventilation ($p=1.000$) and mortality and outcome rates ($p=0.784$) in patients admitted for their first and repeated admissions, there was clearly a strong and significant relationship between ventilator use and mortality ($p<0.01$). Similarly, Joya-Montosa et al. (18) reported that patients with severe CAP who required mechanical ventilation within the first 24 hours of ICU admission had a significantly higher mortality rate compared to those who did not require intubation (47.2% vs. 19%, $p=0.002$).

Study Limitations

This study has several limitations that should be acknowledged. First, the single-center, retrospective design limits the external validity of our findings, as the results may not fully represent the heterogeneity of patient populations, healthcare systems, and clinical practices in other settings. Retrospective analyses are also inherently vulnerable to selection bias, and they preclude definitive conclusions about causality between predictors and outcomes.

Second, reliance on electronic medical records may have introduced information bias due to incomplete or inconsistent documentation. Important clinical variables, such as the timing of symptom onset, delays in initiation of antibiotic therapy, vaccination history, socioeconomic status, and access to outpatient care, were not systematically captured, which restricted our ability to evaluate their influence on patient outcomes.

Third, although we examined individual clinical and laboratory parameters, we did not perform multivariable analyses such as logistic regression, which could have helped identify independent predictors and adjust for potential confounders. The absence of such analyses may have limited the robustness of our conclusions regarding risk factors.

Finally, the relatively modest sample size reduced statistical power, particularly for subgroup analyses, and may have limited the precision of effect estimates. For these reasons, our findings should be interpreted with caution, and future large-scale, multicenter, prospective studies with standardized data collection and the application of advanced statistical methods are necessary to validate and extend these observations.

Future Research

Future research will be critical to achieving a more comprehensive understanding of the clinical course and mortality risk factors in patients with CAP. First, multicenter and prospective studies are needed to capture differences across diverse patient populations and healthcare systems, thereby improving the generalizability of findings. Larger sample sizes will also increase statistical power and strengthen the reliability of results.

In addition, incorporating variables such as the timing of symptom onset, treatment delays, socioeconomic status, vaccination history, and access to outpatient care into future study designs will provide a more holistic view of the determinants of disease progression. The application of advanced statistical approaches, including logistic regression and multivariable modeling, will help identify independent predictors and support the development of more targeted clinical decision-making strategies.

Moreover, prospective evaluation of the association between invasive mechanical ventilation and mortality may contribute to optimizing intensive care management in these patients. Similarly, long-term follow-up studies investigating the relationship between repeated hospital admissions and clinical outcomes would help clarify the natural course of the disease and treatment responses.

Ultimately, larger, multicenter, and methodologically rigorous studies are essential to validate current findings and to generate robust evidence that can guide clinical practice in the management of CAP.

Conclusion

In our study, in which we evaluated the past two-year period in a single-center, no significant difference was found between the first and second admissions with the diagnosis of CAP in terms of age, gender, comorbidities, CURB-65 score, need for intensive care and need for invasive mechanical ventilation. Mortality rates of patients who required only invasive mechanical ventilation were significantly higher than those of patients who did not require intubation ($p<0.01$). The fact that no direct correlation was found between the number of hospital admissions and mortality suggests that repeated hospital admissions do not always result in an unfavorable disease course. However, the fact that our data are the product of a single-center study and are based on a limited sample size limits the generalizability of the study results.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital (decision no: 2024/97, date: 26.06.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Original Article

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Assessment of Serum Adropin Levels in Patients with Subclinical Hypothyroidism

Subklinik Hipotiroidili Hastalarda Serum Adropin Düzeyinin Araştırılması

Tuba YILMAZ YILDIRIM[1], Mehmet ZORLU[2], Eray Metin GÜLER[3], Muharrem KISKAÇ[2], Hakan BEYAZTAŞ[4]

[1]Marmara University Faculty of Medicine, Department of Gastroenterology, İstanbul, Türkiye
[2]Bezmialem Vakıf University Faculty of Medicine; Prof. Dr. Muharrem Kıskaç Private Clinic, Department of Internal Medicine, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, Department of Medical Biochemistry, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Department of Medical Biochemistry İstanbul, Türkiye

ABSTRACT

Objective: Subclinical hypothyroidism (SCH) is defined as elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) and free triiodothyronine (FT3) levels. This study aimed to evaluate serum adropin levels in patients with SCH.

Methods: This prospective cross-sectional study included 41 patients with SCH and 43 euthyroid controls. Thyroid function tests, biochemical parameters, and serum adropin levels were measured using ELISA. The groups were statistically compared.

Results: No significant differences were observed between the groups regarding age, gender, or body mass index ($p>0.05$). Serum adropin levels were significantly lower in the SCH group compared to the control group (136.75±41.87 ng/mL vs. 220.65±64.93 ng/mL; $p<0.001$). A significant negative correlation was detected between adropin and TSH levels ($r=-0.765$; $p<0.001$), whereas no significant correlation was found with FT3 or FT4.

Conclusion: Serum adropin levels were significantly decreased in patients with SCH. Adropin may potentially serve as a biomarker for cardiometabolic risk assessment in SCH.

Keywords: Adropin, subclinical hypothyroidism, metabolic syndrome, insulin resistance

ÖZ

Amaç: Subklinik hipotiroidi (SKH), serum tiroid uyarıcı hormon (TSH) düzeylerinin yüksek, serbest tiroksin (FT4) ve serbest triiyodotironin (FT3) düzeylerinin ise normal olduğu bir durumdur. Bu çalışmanın amacı, SKH hastalarında serum adropin düzeylerini değerlendirmektir.

Yöntemler: Bu prospektif kesitsel çalışmaya 41 SKH hastası ve 43 ötiroid kontrol dahil edildi. Katılımcıların tiroid fonksiyon testleri, biyokimyasal parametreleri ve serum adropin düzeyleri ELISA yöntemi ile ölçüldü. Gruplar istatistiksel olarak karşılaştırıldı.

Bulgular: Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi açısından anlamlı fark saptanmadı ($p>0,05$). SKH grubunda serum adropin düzeyi kontrol grubuna göre anlamlı olarak düşük bulundu (136,75±41,87 ng/mL'ye karşı 220,65±64,93 ng/mL; $p<0,001$). Adropin ile TSH arasında anlamlı negatif korelasyon saptandı ($r=-0,765$; $p<0,001$). FT3 ve FT4 ile anlamlı korelasyon izlenmedi.

Sonuç: SKH'li hastalarda serum adropin düzeyi anlamlı derecede düşüktür. Adropin, SKH'de kardiyometabolik riskin değerlendirilmesinde potansiyel bir biyobelirteç olabilir.

Anahtar Kelimeler: Adropin, subklinik hipotiroidi, metabolik sendrom, insülin direnci

Address for Correspondence: Tuba Yılmaz Yıldırım MD, Marmara University Faculty of Medicine, Department of Gastroenterology, İstanbul, Türkiye
E-mail: tuba_yilmaz83@hotmail.com
ORCID IDs of the authors: T.Y.Y.: 0000-0003-0753-5385, M.Z.: 0000-0003-4867-4859, E.M.G.: 0000-0003-4351-1719, M.K.: 0000-0003-2534-2675, H.B.: 0000-0003-3706-5193

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Introduction

The thyroid gland secretes thyroid hormones, which are crucial for the formation and growth of every physiological cell and for regulating metabolism (1). These metabolic effects at the tissue level are mediated by transmembrane transporters, deiodinases, and thyroid hormone receptors (2). Subclinical hypothyroidism (SCH) is characterized by normal peripheral free thyroxine (FT4) and free triiodothyronine (FT3) levels but an elevated serum concentration of thyroid-stimulating hormone (TSH). SCH affects approximately 4-20% of adults, with a higher prevalence in areas with iodine deficiency (3,4). The condition is found in 4-10% of the general population and 7-26% of the elderly, and it can progress to overt hypothyroidism (5-7). SCH is sometimes considered an early stage of hypothyroidism and has been associated with endothelial dysfunction, metabolic syndrome, insulin resistance, atherosclerosis, and cardiovascular diseases (CVD). By reducing nitric oxide (NO) synthesis and release, promoting the development of atheromatous plaque, and impairing endothelial function, research indicates that SCH may play a role in the development of ischemic heart disease (8). The liver and brain are the primary sites of expression for the peptide adropin, which is encoded by the *energy homeostasis-associated (ENHO)* gene. It is also generated in other organs, including the heart, kidneys, pancreas, and gastrointestinal tract (9). Adropin plays a key role in regulating endothelial function, reducing insulin resistance, limiting angiogenesis, and maintaining the balance of fats and carbohydrates. Low level of adropin levels have been linked to various metabolic and cardiovascular disorders, such as obesity, diabetes, hypertension, endothelial dysfunction, cerebrovascular diseases, and metabolic syndrome. Increased levels of adropin are associated with elevated NO levels that promote arterial stiffness via NO-dependent signaling (10,11). Given their associations with chronic conditions like diabetes, CVDs, and endothelial dysfunction, the possible link between SCH and serum adropin levels merits more research. There aren't many studies that look into this relationship. The principal objective of our research is to ascertain whether patients with SCH have changed serum adropin levels and whether adropin may be a valuable intermediate marker for the pathophysiology and clinical outcomes of this condition.

Methods

Study Group

This prospective, cross-sectional, case-controlled study received approval from the Bezmialem Vakıf University Faculty of Medicine Ethics Committee (decision no: 2/16; reference no: E-71306642-050.05.04-9611, date: 24.02.2021). Every participant who took part in the study gave written informed consent.

Inclusion and Exclusion Criteria

The study enrolled 41 adult patients with SCH and 43 age- and gender-matched euthyroid individuals (controls) from the outpatient clinic at Bezmialem Vakıf University. SCH was diagnosed based on elevated TSH levels above the upper normal limit, with normal FT4 levels. To account for potential TSH fluctuations, measurements were repeated within 1-3 months. Participants with normal thyroid function test results were assigned to the healthy control group.

For patients with SCH, the TSH reference range was defined as 4-10 mIU/L, while euthyroid individuals were considered to have TSH levels <4 mIU/L. The laboratory reference ranges were as follows; TSH: 0.35-4.94 mIU/L; FT4: 9-19 pmol/L; and FT3: 2.42-6 pmol/L. Individuals aged ≤65 years were included. Exclusion criteria comprised diabetes mellitus, hypertension, CVD, use of medications affecting thyroid function (including steroids, amiodarone, and lithium), pituitary disorders, familial hyperlipidemia, renal or hepatic dysfunction, infectious diseases (local or systemic), neoplasms, inflammatory conditions (acute or chronic), alcohol or tobacco consumption, pregnancy, lactation and morbid obesity.

Blood Assay

Venous blood samples for biochemical and adropin analyses were collected from all participants in gel tubes between 08:00 and 09:00 AM following a 12-hour fasting period. The process of acquiring serum involved centrifuging the samples at a rotational speed of 3600 revolutions per minute for a duration of 10 minutes. Subsequently, the obtained serum samples were transferred into Eppendorf tubes and preserved at a temperature of -80 degrees celsius until the time of analysis. The levels of adropin in the serum were determined utilizing the Human Adropin ELISA Kit, manufactured by BTLab, China (E3231Hy). All participants had their weight and height measured; weight was expressed in kilograms and height in centimeters. The following formula was used to calculate the body mass index (BMI):

$$\boxed{\text{BMI} = \frac{[\text{weight (kg)}]}{[\text{height}^2(\text{m}^2)]}}$$ (12).

Statistical Analysis

The analysis of the data was done with SPSS (IBM Statistics v. 22 points 0). The mean and standard deviation were computed as descriptive statistics. One-way analysis of variance was utilized to compare multiple variables. For data that were normally distributed, Pearson's correlation analysis was used, and for data that were not, Spearman's correlation analysis was used. The threshold for statistical significance was set at $p<0.05$, with a 95% confidence interval.

Results

The mean age of the 84 volunteers included in the study was 36.48±11.99 years in the SCH group (male: 8; female: 33) and 33.97±9.65 years in the control group (male: 9; female: 34). In the SCH and the control groups,

the mean BMI was 24.62±4.04 kg/m² and 23.50±2.52 kg/m², respectively. According to Table 1, there were no statistically significant differences between the groups in terms of age or BMI (p>0.05). The TSH level was significantly higher in the SCH group (6.47±1.36 mIU/L) than in the control group (2.02±0.86 mIU/L) (p<0.001). However, no significant difference was observed in mean FT4 and FT3 levels between the groups (SCH group: 11.73±1.32 pmol/L, 4.48±0.75 pmol/L; control group: 12.24±1.26 pmol/L, 4.42±0.50 pmol/L, respectively) (p>0.05) (Table 1).

A statistically significant negative correlation was observed between adropin and TSH levels in the regression analysis (p<0.001). However, adropin levels did not show significant correlations with FT3 or FT4 levels (p>0.05) (Figure 1). Additionally, adropin levels were not significantly associated with age, BMI, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglyceride (TG) levels (p>0.05) (Table 1). Similarly, regression analysis demonstrated an inverse relationship between adropin and TSH levels, while no meaningful correlations were identified with FT3, FT4, age, BMI, TC, LDL-C, or TG levels (p>0.05) (Table 1).

A significant decrease in serum adropin levels was observed in the SCH group (136.75±41.87 ng/mL) relative to the control group (220.65±64.93 ng/mL) (p<0.001) (Figure 1). Adropin levels were found to be low in patients with SCH. In hypothyroidism, energy expenditure decreases, metabolic rate decreases, and adropin synthesis is suppressed.

In SCH, NO synthesis decreases. Adropin protects endothelial function, and low levels may be both a cause and a consequence of endothelial dysfunction.

Routine biochemical measures showed no significant differences between the groups (p>0.05), according to Table 2.

Table 1. Comparison of TSH, FT3, FT4, adropin and other biochemical parameters in SCH group and healthy control subjects

	Group 1 SCH group n=41 mean ± SD	**Group 2 healthy control group n=43 mean ± SD**	**p-value**
Age (year)	36.48±11.99	33.97±9.65	0.293
BMI (kg/m²)	24.62±4.04	23.50±2.52	0.130
Glucose (mg/dL)	91.92±10.85	91.34±9.86	0.799
Creatinine (mg/dL)	0.73±0.11	0.75±0.16	0.497
ALT (U/L)	18.85±9.59	17.83±11.01	0.654
AST (U/L)	27.29±48.33	17.79±4.56	0.203
GGT (U/L)	26.04±17.89	20.04±18.19	0.132
ALP (U/L)	76.00±24.87	67.86±18.87	0.094
CK (U/L)	63.82±26.97	70.69±36.81	0.334
Ca (mg/dL)	9.18±0.47	9.31±0.25	0.130
FT3 (pmol/L)	4.48±0.75	4.42±0.50	0.674
FT4 (pmol/L)	11.73±1.32	12.24±1.26	0.075
TSH (mIU/L)	6.47±1.36	2.02±0.86	**<0.001***
HbA1c (%)	5.01±0.38	5.14±0.31	0.100
HOMA-IR	2.10±1.23	2.63±2.61	0.240
TC (mg/dL)	180.29±46.3	193.65±46.25	0.190
LDL-C (mg/dL)	107.80±35.54	122.90±44.03	0.088
Triglyceride (mg/dL)	117.29±68.68	112.48±70.03	0.752
Fe (µg/dL)	70.80±33.63	63.79±30.13	0.317
TIBC	312.02±56.15	337.48±60.12	0.057
WBC (10³/µL)	7394.63±2007.48	7601.44±1967.82	0.635
Hg (gr/dL)	12.81±1.48	12.85±1.55	0.907
HCT (%)	39.63±3.94	38.83±4.01	0.362
PLT (10³/µL)	258.75±69.24	250.60±50.83	0.548
Adropin (ng/mL)	136.75±41.87	220.65±64.93	**<0.001***

*: Statistically significant, SD: Standard deviation, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamagglutamyl transferase, ALP: Alkaline phosphatase, CK: Creatine kinase, Ca: Calcium, FT3: Free thyroiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostatic model evaluation-insulin resistance, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, Fe: Iron, TIBC: Total iron binding capacity, WBC: White blood cell, Hg: Hemoglobin, HCT: Hematocrit, PLT: Platelet

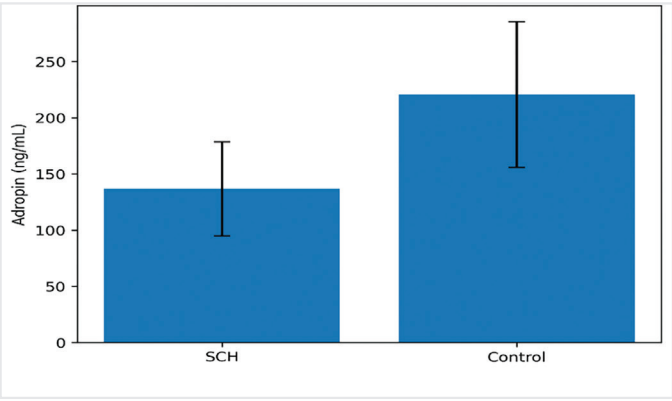

Figure 1. Adropin distribution according to groups
SCH: Subclinical hypothyroidism

Table 2. Evaluation of the relationship between adropin and age, BMI and laboratory results in the SCH and control groups

	Correlation coefficient (R)	p-value
Age	0.05	0.967
BMI	-0.141	0.202
Glucose (mg/dL)	0.015	0.891
Creatinine (mg/dL)	0.155	0.159
FT3 (pmol/L)	-0.033	0.765
FT4 (pmol/L)	0.075	0.496
TSH (mIU/L)	-0.765	**<0.001***
TC (mg/dL)	0.082	0.458
LDL-C (mg/dL)	0.118	0.284
Triglyceride (mg/dL)	-0.011	0.923
HOMA-IR	-0.089	0.419

*: Statistically significant; SCH: Subclinical hypothyroidism, BMI: Body mass index, FT3: Free thyroiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HOMA-IR: Homeostatic model evaluation- insulin resistance

Discussion

This study evaluated serum adropin levels in patient with SCH and compared them with euthyroid controls. In addition, we investigated the relationship between adropin levels and anthropometric, metabolic, and biochemical parameters. To minimize potential confounding effects, the groups were closely matched in terms of age, gender, and BMI. No significant differences were observed between the groups regarding BMI, homeostatic model evaluation-insulin resistance, or HbA1c levels. Given the limited number of studies examining the association between SCH and adropin, our primary objective was to determine whether serum adropin levels differ in patients with SCH. We demonstrated a significant reduction in serum adropin levels in the SCH group, accompanied by a strong negative correlation between adropin and TSH levels. These findings suggest a potential interaction between thyroid function and adropin metabolism. Thyroid hormone receptors are present in vascular endothelial and myocardial tissues, indicating an important role of thyroid hormones in cardiovascular regulation. SCH has been associated with endothelial dysfunction, insulin resistance, dyslipidemia, and increased cardiovascular risk (13-17). Adropin, which regulates lipid and glucose homeostasis, has been shown to enhance endothelial nitric oxide synthase expression and support endothelial function (9-11). Topuz et al. (18) found lower serum adropin levels in patients with type 2 diabetes mellitus (T2DM) with endothelial dysfunction, suggesting adropin as a marker for endothelial dysfunction. Similarly, Zang et al. (19) reported reduced adropin levels in overweight/obese patients with T2DM, linking it to insulin sensitivity and glucolipid homeostasis. Zheng et al. (20) found significantly lower adropin levels in patients with CAD, especially those with acute myocardial infarction or angina. Unlike previous studies, we focused on patients with SCH without chronic conditions such as hypertension, diabetes, or CAD. Serum adropin levels were 136 ng/mL in patients with SCH versus 229 ng/mL in controls, a significant difference consistent with prior findings. We propose that thyroid hormones influence *ENHO* gene expression in adropin-synthesizing tissues. Additionally, reduced adropin may contribute to CVD, insulin resistance, and endothelial dysfunction in SCH. Rezk and Atia (21) studied hypothyroid-induced rats and found significantly lower adropin levels in those that gained weight, along with increased LDL, very low-density lipoprotein (VLDL), and TGs. Adropin negatively correlated with LDL, VLDL, and TG, while positively correlating with HDL and FT3 (21). Unlike this study, our research focused on patients with SCH with similar BMI, finding no significant differences in lipid profiles, likely due to sample size limitations. Mogulkoc et al. (22) found lower adropin levels in both hypothyroid and hyperthyroid rats, suggesting thyroid dysfunction altered adropin metabolism. We hypothesize that SCH-related metabolic changes similarly affect adropin secretion through direct or indirect mechanisms. Akbaba et al. (23) compared adropin levels between patients with SCH, patients with overt hypothyroidism, and controls, finding lower adropin in hypothyroid groups, though not statistically significant. Overall, our findings support the hypothesis that thyroid function may influence adropin regulation through direct or indirect mechanisms. However, larger, multicenter studies are required to clarify the underlying molecular pathways and to determine whether adropin can serve as a reliable biomarker in patients with SCH.

Study Limitations

There are several limitations to our study. First, the study only included a small sample size and was carried out in one place, which might have limited how broadly the results could be applied. Second, there was an imbalance in gender distribution, with a higher number of female participants

compared to males. However, a strength of our study was that key demographic parameters, including age, gender, and BMI, were closely matched between the groups.

Conclusion

Patients with SCH had significantly lower serum adropin levels than the control group. This suggests that thyroid hormone levels may regulate adropin synthesis, possibly through direct or indirect effects on *ENHO* gene expression. Our hypothesis and objective is to determine whether adropin levels can be used as a marker for early detection of ischemic heart disease and metabolic heart disease in patients with SCH. Adropin can be useful in the early diagnosis and treatment of metabolic diseases that may develop as a precursor to hypothyroidism. Larger multicenter studies are needed to clarify the underlying mechanisms.

Ethics

Ethics Committee Approval: This prospective, cross-sectional, case-controlled study received approval from the Bezmialem Vakıf University Faculty of Medicine Ethics Committee (decision no: 2/16; reference no: E-71306642-050.05.04-9611, date: 24.02.2021).

Informed Consent: Every participant who took part in the study gave written informed consent.

Footnotes

This research is derived from the medical specialty thesis of Tuba Yılmaz Yıldırım.

Authorship Contributions

Design: T.Y.Y., M.Z., H.B., Data Collection or Processing: T.Y.Y., M.Z., Analysis or Interpretation: E.M.G., M.K., Literature Search: T.Y.Y., M.Z., E.M.G., Writing: T.Y.Y., M.Z.

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

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Original Article

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Evaluation of the Thoughts of Medical Faculty Members About Pre-graduation Medical Education

Tıp Fakültesi Öğretim Üyelerinin Mezuniyet Öncesi Tıp Eğitimi ile İlgili Düşüncelerinin Değerlendirilmesi

Yasemin DURDURAN[1], Mehtap YÜCEL[1], Mehmet UYAR[2], Esra HACILAR[3], Şükrü Nail GÜNER[4]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Public Health, Department of Medical Education and Informatics, Konya, Türkiye
[2]Necmettin Erbakan University Meram Faculty of Medicine, Department of Public Health, Konya, Türkiye
[3]Provincial Health Directorate, Yozgat, Türkiye
[4]Necmettin Erbakan University Meram Faculty of Medicine, Department of Child Health and Diseases, Division of Pediatric Allergy and Immunology, Konya, Türkiye

ABSTRACT

Objective: This study aims to explore the views of faculty members regarding undergraduate medical education at their institution and to gather their suggestions for improving the quality of medical training.

Methods: This descriptive study was conducted with 178 faculty members from a university's medical school. Data were collected using a structured questionnaire that included items on demographics, professional background, and perspectives on medical education. Descriptive statistics were used for data analysis.

Results: Among the participants, 98.3% had attended at least one education-related course, with the most common being training for trainers (88.6%). While 39.9% had not served on any educational committee, 42.7% had not participated in problem-based learning scenario writing. The majority identified increasing student numbers (93.8%) and declining societal respect for physicians and reduced student motivation (87.1%) as major issues in medical education.

Conclusion: To enhance the quality of undergraduate medical education, it is essential to increase faculty involvement, promote participation in educational development activities, improve teaching strategies, and regulate student intake.

Keywords: Education, medical education, medical school

ÖZ

Amaç: Bu çalışmanın amacı, bir tıp fakültesinde görev yapan öğretim üyelerinin mezuniyet öncesi tıp eğitimine ilişkin görüşlerini belirlemek ve tıp eğitiminin geliştirilmesine yönelik önerilerini ortaya koymaktır.

Yöntemler: Tanımlayıcı nitelikteki bu çalışma, bir üniversitenin tıp fakültesinde görev yapan 178 öğretim üyesi ile yürütülmüştür. Katılımcılara, demografik özellikler, mesleki bilgiler ve tıp eğitimiyle ilgili sorulardan oluşan yapılandırılmış bir anket uygulanmıştır. Veriler tanımlayıcı istatistiklerle analiz edilmiştir.

Bulgular: Katılımcıların %98,3'ü en az bir eğitimle ilgili kursa katıldığını belirtmiş; en yaygın katılım, %88,6 ile eğitici eğitimi kursuna olmuştur. Öğretim üyelerinin %39,9'u herhangi bir eğitim kurulunda görev almadığını, %42,7'si ise probleme dayalı öğrenme senaryo yazımında yer almadığını ifade etmiştir. Katılımcıların %93,8'i tıp fakültelerine alınan öğrenci sayısındaki artışı, %87,1'i ise toplumda hekim saygınlığının azalmasıyla öğrencilerin motivasyonunun düşmesini önemli bir sorun olarak değerlendirmiştir.

Sonuç: Tıp eğitiminde kaliteyi artırmak için öğretim üyelerinin eğitime aktif katılımı teşvik edilmeli, eğitici gelişim programları yaygınlaştırılmalı, öğretim yöntemleri çeşitlendirilmeli ve öğrenci kontenjanları daha dengeli planlanmalıdır.

Anahtar Kelimeler: Eğitim, tıp eğitimi, tıp fakültesi

Address for Correspondence: Asst. Prof., Mehtap Yücel, Necmettin Erbakan University Meram Faculty of Medicine, Department of Public Health, Department of Medical Education and Informatics, Konya, Türkiye
E-mail: mhtpyucel@hotmail.com
ORCID IDs of the authors: Y.D.: 0000-0003-0455-0627, M.Y.: 0000-0001-6091-3205, M.U.: 0000-0002-3954-7471, E.H.: 0000-0001-8914-8199, Ş.N.G.: 0000-0002-8860-6132

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Introduction

Medical education is a dynamic process that is not limited to the transfer of professional knowledge and skills, but also aims to produce qualified physicians, taking into account the needs of society. This process should be constantly changing and evolving under the influence of many different factors, such as the country's health priorities, health policy, rapidly developing science and technology, and innovations in educational science. Training physicians who can provide qualified health services directly affects the quality of medical education, and this quality plays a crucial role in the overall success of the health system (1-3).

In recent years, important studies have been carried out to improve the quality of medical education in Türkiye. Among these studies, the accreditation process carried out by the Association for Evaluation and Accreditation of Medical Education Programs (TEPDAD) and the National Core Education Program, which was prepared to ensure the standardisation of undergraduate medical education, have an important place (4-6).

The National Medical Education Accreditation Board (UTEAK), one of the bodies of TEPDAD, has undertaken a guiding role in aligning the educational programs of medical schools with national and international standards. UTEAK evaluates and accredits the educational programs of applicant medical schools based on nine main headings prepared in line with national requirements together with internationally accepted standards (7). These standards are listed as aims and objectives, educational program, evaluation of students, students, program evaluation, teaching staff, educational resources and opportunities, management and execution, continuous renewal and development (7,8).

In particular, the "programme evaluation" standard requires that medical schools have a system in place that can monitor the effectiveness of the educational programme and provide feedback to strengthen the programme. This system requires the use of quantitative and qualitative methods, such as cross-sectional or continuous data collection, analysis and interpretation when evaluating the programme (1,8). Obtaining educators' opinions is an integral part of the programme evaluation process and is considered an important feedback mechanism for improving the quality of education (8-10). In this context, it would be valuable to obtain the opinions and suggestions of faculty members in order to improve the educational standards of medical schools.

The aim of this study is to examine the views of faculty members working in medical schools regarding current medical education programmes, including their perspectives on the aims of medical education and the problems encountered in the process. The study also seeks to support efforts to improve the quality of medical education by considering faculty members' experiences and solution-oriented suggestions.

Methods

Participants

The universe of this descriptive study consists of the faculty members of the Faculty of Medicine of Necmettin Erbakan University (NEU). During this study, which was conducted between May and June 2024, a total of 255 faculty members were employed in this faculty of medicine, including 134 professors (Prof. MD), 82 associate professors (Assoc. Prof. MD), and 39 assistant professors (Assoc. Prof.). The sample size was not calculated in advance because the study aimed to reach the entire population of faculty members at the institution. Faculty members who were currently working at the faculty of medicine and who volunteered to participate in the study and gave their consent were included. Those with missing data in the data collection form were not included in the study. A total of 178 faculty members were included in the study, including 82 professors, 70 associate professors and 26 assistant professors.

Ethical Approval

This study was approved by the NEU Non-Drug and Medical Device Research Ethics Board (decision no: 2024/5027, date: 07.06.2024). Informed consent was obtained from all participants prior to participation.

Data Collection Forms

Form with Demographic and Work-related Questions

This form asks about the demographic characteristics of the participants, such as age, gender and marital status. In addition, this form includes work-related questions such as title, work status in basic medical-surgical sciences, years of work as a faculty member, and years of work as a faculty member at the NEU Faculty of Medicine.

Form Containing Questions that may be Related to Medical Education

The data collection form, which was prepared by reviewing the literature, includes questions related to medical education, such as whether faculty members have previously attended courses related to education and served on committees related to education, the years of courses they have given at the faculty of medicine, and the methods/techniques used in teaching. In addition, this form includes questions prepared in a 3-point Likert structure (agree/undecided/disagree) that evaluate the purpose of medical education and the problems in medical education. In the last part of the form, open-ended questions were asked to get the opinion of the faculty members about the courses they think should be added to the curriculum in order to improve medical education and what can be done to overcome the problems in medical education.

Methodology

The data collection process took place between 20 June and 10 July. The study was conducted through a web-based questionnaire administered via a secure online data collection platform. A link to participate in the study was shared with groups of faculty members at the NEU Faculty of Medicine, and reminders were made through weekly announcements. Before the first link was shared, preliminary information about the study was provided through a message sent to faculty members by the dean's office, and as the study was based on voluntary participation, those who agreed were asked to complete the form.

Statistical Analysis

The statistical analysis of the results obtained in the study was carried out using the programme SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, US). Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, 1-3 quartiles) were used to evaluate the research data.

Results

The mean age of the 178 faculty members included in the study was 47.77±8.11 years, 66.3% were male, and 94.4% were married. Of the participants 46.1% were professors and 53.4% worked in internal medicine. The median tenure of the participants as a faculty member was 11 (6-17) years, while the median tenure of the participants as a faculty member at NEU Faculty of Medicine was determined to be 10 (6-14) years (Table 1).

Of the faculty members 98.3% stated that they had attended a course related to education, with the most being training of trainers at 88.6%. It was determined that 39.9% of the participants did not serve on any board related to education, and 42.7% did not participate in writing the scenarios used in any problem-based learning (PBL) sessions. The teaching method and technique most frequently used by faculty members in medical education was the lecture method with 96.6%, and the most frequently used training technique was question-answer with 97.8%. In order to create a positive atmosphere during the training process, 87.1% stated that they made eye contact and 81.5% stated that they made motivating/interesting introductions to the topics (Table 2).

It was found that 62.9% of the faculty members were undecided/disagree with the statement that the purpose of medical education is to train good health managers, 42.1% with the statement that it is to train students who are successful in the medical specialty examination, and 32.6% with the statement that it is to meet the country's need for doctors (Table 3).

It was found that 85.4% of the faculty members were undecided/disagreed with the statement that there is no problem in the medical education process. 93.8% of the participants stated that the increase in the number of students accepted to medical schools was a problem, and 87.1% stated that the decrease in the prestige of doctors in society and the decrease in the motivation of medical students was a problem (Table 4).

Of the 102 faculty members who responded to the question "What courses do you think should be included in medical schools in addition to medical courses?" 53.9% said that communication skills, 20.6% medical law, 20.6% foreign languages, art education should be added to medical education. Of the 65 participants who made suggestions for overcoming the problems in medical education, 40.0% said that the number of medical schools and the number of students should be reduced, 23.1% said that the performance system of faculty members should be reorganised, and 21.5% said that the quality of faculty members should be improved (Table 5).

Discussion

This study found that nearly all of the 178 participating faculty members had attended at least one course related to medical education. The most frequently attended courses were "training of trainers" and "PBL" courses, whereas participation in courses on assessment, evaluation, and question preparation was lower. A previous report from the same medical school (2011-2012) indicated that 158 faculty members had taken a PBL course during that period (11). Similarly, another study showed that all faculty members had received training of trainers, the majority had taken PBL courses, and fewer had participated in assessment-

Table 1. Demographic and work-related characteristics of participants (n=178)

Variables	All participants
Age/mean ± SD	47.77±8.11
Gender, n (%)	
Female	60 (33.7)
Male	118 (66.3)
Marital status, n (%)	
Married	168 (94.4)
Single	10 (5.6)
Title, n (%)	
Prof. MD	82 (46.1)
Assoc. Prof. MD	70 (39.3)
Assistant professor	26 (14.6)
Medical science in which your department is located/n (%)	
Internal medical sciences	95 (53.4)
Surgical medical sciences	58 (32.6)
Basic medical sciences	25 (14.0)
Years of service as a faculty member/median (25th and 75th percentiles)	11 (6-17)
Years of service as a faculty member at NEU Faculty of Medicine/median (25th and 75th percentiles)	10 (6-14)

SD: Standard deviation, NEU: Necmettin Erbakan University

related courses (12). These findings suggest that faculty members are interested in educational development and that the institution supports such initiatives. Expanding training opportunities in measurement, evaluation, and question writing may further improve educational quality, particularly in assessing students' knowledge and competencies.

Nearly half of the participants in this study had not served on any education-related board and had not been involved in writing PBL scenarios. Other studies reported

Table 2. Distribution of participants' responses to questions that may be related to medical education (n=178)

Variables		All participants n (%)
Participation in training-related courses (training of trainers. preparation of questions etc.)	Yes	175 (98.3)
	No	3 (1.7)
Types of training courses attended (n=175)*	PBL	152 (86.9)
	Training of trainers	155 (88.6)
	Assessment-evaluation	39 (22.3)
	Question preparation	42 (24.0)
	Other	3 (1.7)
Status of participation in any faculty committee related to education	Currently serving on an education-related board	49 (27.5)
	Previously served on an education-related board	58 (32.6)
	Never served	72 (39.9)
The status of participation in any "PBL scenario" software	Yes	102 (57.3)
	No	76 (42.7)
The years covered by the courses given by the department in medical education	Only preclinical years (first 3 years)	34 (19.1)
	Only clinical period (years 4-6)	47 (26.4)
	Both preclinical and clinical period	97 (54.5)
The existence of responsible courses other than the basic courses of the department (PBL etc.)	Yes	106 (59.6)
	No	72 (40.4)
The teaching methods and techniques they use in medical education*	Narrative method	172 (96.6)
	Case study method	128 (71.9)
	Problem solving method	95 (53.4)
	Discussion method	122 (68.5)
	Demonstration method	78 (43.8)
The teaching techniques they use in medical education*	Question-answer	174 (97.8)
	Brainstorming	108 (60.7)
	Role-play	24 (13.5)
	Case study	119 (66.9)
	Group studies	65 (36.5)
	Demonstration	74 (41.6)
	Coaching	36 (20.2)
The methods they use to create a positive educational atmosphere during the educational process (course/clerkship/training)*	Identify needs before lesson/exercise/course	69 (38.8)
	Planning lessons according to adult learning principles	75 (42.1)
	Carry out introduction/warm-up exercises	97 (54.5)
	Making motivating/interesting introductions to topics	145 (81.5)
	Use an appropriate tone of voice	129 (72.5)
	Use appropriate and non-technical language	92 (51.7)
	Using body language that is open to communication	122 (68.5)
	Making eye contact	155 (87.1)
	Using interactive teaching methods	138 (77.5)

*: Respondents indicated more than one option, PBL: Problem-based learning

participation in educational boards ranging between 57.5% and 67.6% (13,14). Involvement in educational committees contributes to the professional development of faculty and enhances the overall quality of education. Similarly, increasing faculty participation in PBL scenario development could diversify content and improve faculty engagement with the PBL method.

Regarding instructional approaches, faculty members most frequently used lecture-based teaching and least frequently employed demonstration techniques. Among active

Table 3. Distribution of participants' responses to written statements about the purpose of medical education (n=178)

The purpose of medical education*	All participants	
	Agree	Undecided/disagree
	n (%)	n (%)
Embrace the continuity of medical education	169 (94.4)	9 (5.1)
To teach how to access up-to-date information	171 (96.1)	7 (3.9)
Encourage scientific research	153 (86.0)	25 (14.0)
Demonstrate the importance of teamwork	167 (93.8)	11 (6.2)
Motivate interdisciplinary and inter-professional work	173 (97.2)	5 (2.8)
To train doctors to provide quality health services	175 (98.3)	3 (1.7)
To produce qualified general practitioners	164 (92.1)	14 (7.9)
To produce doctors who understand primary care	164 (92.1)	14 (7.9)
To produce successful candidates for specialty examinations	103 (57.9)	75 (42.1)
To produce doctors with the required level of professional knowledge and skills	149 (83.7)	29 (16.3)
To serve public health	172 (96.6)	6 (3.4)
To produce good health managers	66 (37.1)	112 (62.9)
To produce doctors who are good communicators	170 (95.5)	8 (4.5)
To produce doctors who are good decision-makers	172 (96.6)	6 (3.4)
To meet the country's need for doctors	120 (67.4)	58 (32.6)
To produce doctors who integrate knowledge and think critically	169 (94.9)	9 (5.1)

*: Respondents indicated more than one option

Table 4. Distribution of participants' responses about medical education (n=178)

Expressions*	All participants	
	Agree	Undecided/disagree
	n (%)	n (%)
There is no problem in the medical education process	26 (14.6)	152 (85.4)
There is a problem of lack of standardisation in medical school education	137 (77.0)	41 (23.0)
The large number of medical schools is a problem	152 (85.4)	26 (14.6)
The time spent by faculty members on teaching is less than the time spent on diagnosing and treating patients which disrupts teaching	127 (71.3)	51 (28.7)
The scarcity/ignorance of techniques used in education affects the quality of education	138 (77.5)	40 (22.5)
The scarcity/inadequacy of educational materials is a problem	87 (54.5)	81 (45.5)
Insufficient time for practical training is a problem	103 (57.9)	75 (42.1)
The increase in the number of students admitted to medical schools is a problem	167 (93.8)	11 (6.2)
The excessive number of course hours and the burden of unnecessary information in addition to the necessary information for the profession are problems	90 (50.6)	88 (49.4)
The decline in the reputation of the doctor in society and the decline in the motivation of medical students are problems	155 (87.1)	23 (12.9)
The different expectations of students and faculty members are problems	141 (79.2)	37 (20.8)
Communication problems between students and faculty members negatively affect education	131 (73.6)	47 (26.4)

*: Respondents indicated more than one option

Table 5. Opinions of faculty members on additional courses they think should be included in medical courses and what can be done to overcome problems in medical education (n=178)

Expressions*	All participants n (%)
Which courses do you think should be compulsory in medical schools in addition to medical courses? (n=102)	
Communication skills	55 (53.9)
Medical law	21 (20.6)
Additional courses such as language arts	21 (20.6)
Psychology courses	9 (8.8)
Health administration-management	6 (5.9)
Scientific writing-statistics	5 (4.9)
What do you think can be done to overcome the problems in medical education? (n=65)	
Reduce the number of medical schools and students	26 (40.0)
Reorganise the faculty performance system	15 (23.1)
Improve the quality of teachers	14 (21.5)
Standardise universities increase financial and moral support for universities	8 (12.3)

*: Respondents indicated more than one option

learning techniques, the question-and-answer method was the most commonly used, while drama and experiential learning methods were the least utilized. A related study found that approximately 80% of instructors used lectures supported by visual materials (9). These findings indicate that innovative teaching methods are still underutilized in medical education. Offering training that showcases the practical application of these methods could enrich the learning experience.

In terms of the objectives of medical education, faculty members showed strong agreement with goals such as training competent doctors who deliver quality care, work collaboratively, stay up to date, serve public health, and make sound decisions. Conversely, there was less agreement with statements about producing good health managers, students successful in the medical specialty exam, and meeting the national physician demand. In a previous study, 57.5% of faculty members stated that the main objective of medical education was to train qualified general practitioners, while only 2.8% cited addressing the country's physician shortage (8). Another study found unanimous agreement on the goal of training "good doctors" (15). These results suggest that faculty members prioritize quality over quantity in medical education.

The vast majority of faculty members agreed that the increasing number of students admitted to medical schools is a major challenge. National and international studies have similarly highlighted this issue (15-17). According to the Health Statistics Yearbook, the number of medical schools increased from 44 in 2002-2003 to 122 in 2022-2023 (18). This growth, along with rising student numbers, may jeopardize the quality of medical education, especially in clinical training, by limiting hands-on learning opportunities and reducing the effectiveness of skill acquisition.

More than half of the faculty members (53.9%) identified communication skills as the most important course to be added to the curriculum. This highlights the importance of non-technical competencies in medical education. Effective communication is essential for the doctor-patient relationship, patient satisfaction, and treatment outcomes (19,20). Medical curricula should therefore include courses beyond biomedical knowledge—such as those in communication, ethics, law, language, and the arts—to develop more empathetic, well-rounded, and socially responsible physicians.

Finally, about one-third of faculty members offered suggestions for improving medical education. Among them, nearly half emphasized reducing the number of medical schools and students, one-quarter highlighted the need to reform the faculty performance system, and one-fifth suggested improving faculty quality. These recommendations point to the need for structural and organizational changes in medical education. Reducing student numbers could allow for more efficient use of resources, while revising performance metrics may encourage faculty to prioritize teaching. These strategies may help make medical education more effective, sustainable, and skill-oriented.

Study Limitations

The study only included faculty members working at one medical school. This limitation may cause the results to differ from the opinions of faculty members working at other medical schools. This limitation means that the results of the study should be interpreted with caution.

Conclusion

This study highlights the active engagement of faculty members in medical education, particularly in trainer

training and PBL courses, while also identifying gaps in participation in assessment-related training and educational committees. Traditional teaching methods still dominate, and there is strong support for incorporating communication skills into the curriculum. To enhance the quality of medical education, efforts should focus on expanding training in evaluation techniques, promoting innovative teaching methods, and addressing systemic issues such as rising student numbers and faculty working conditions.

Ethics

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Non-Drug and Medical Device Research Ethics Board (decision no: 2024/5027, date: 07.06.2024).

Informed Consent: Faculty members who were currently working at the faculty of medicine and who volunteered to participate in the study and gave their consent were included.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.D., M.Y., M.U., E.H., Ş.N.G., Concept: Y.D., M.Y., E.H., Design: Y.D., M.Y., M.U., E.H., Ş.N.G., Data Collection or Processing: Y.D., M.Y., E.H., Ş.N.G., Analysis or Interpretation: Y.D., M.Y., M.U., E.H., Ş.N.G., Literature Search: Y.D., M.Y., E.H., Writing: Y.D., M.Y., M.U., E.H., Ş.N.G.

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

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Original Article

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The Effects of Delivery Room Admission Time on the Labor Process, Neonatal Outcomes, and Women's Traumatic Birth Perceptions: A Comparative Study

Doğumhaneye Kabul Zamanlamasının Doğum Süreci, Yenidoğan Sonuçları ve Kadınların Travmatik Doğum Algısı Üzerine Etkisi: Karşılaştırmalı Bir Çalışma

Hatice Gül ÖZTAŞ[1], Ayşe FİLİZ[2]

[1]Kahramanmaraş Sütçü İmam University Faculty of Health Sciences, Department of Midwifery, Kahramanmaraş, Türkiye
[2]University of Health Sciences Türkiye, Gaziantep City Hospital, Clinic of Obstetric, MSc, Midwife, Gaziantep, Türkiye

ABSTRACT

Objective: This study aimed to investigate the effects of the timing of admission to the delivery room on the labor process, neonatal outcomes, and women's perception of traumatic birth.

Methods: A cross-sectional, comparative study was conducted at a public hospital in southeastern Türkiye between December 2024 and May 2025. A total of 250 pregnant women were divided into two groups based on cervical dilatation at admission: latent phase (n=125) and active phase (n=125).

Results: In the study, obstetric interventions such as bladder catheterisation, oxygen support, episiotomy and continuous fetal monitoring were significantly more common in the latent phase group. However, amniotomy was significantly more frequent in the active phase group. While overall neonatal outcomes showed no significant difference (p>0.05), the 5th-minute Apgar scores and early breastfeeding initiation (within 30 minutes) were significantly higher in the active phase group (p<0.05). Traumatic birth perception scores were notably higher in the latent phase group (p<0.001).

Conclusion: Admission during the latent phase is associated with increased obstetric interventions, with the exception of amniotomy, and higher traumatic birth perception.

Keywords: Admission to delivery room, midwifery, newborn, obstetric interventions, trauma

ÖZ

Amaç: Bu çalışma, doğumhaneye kabul zamanlamasının doğum süreci, yenidoğan sonuçları ve kadınların travmatik doğum algısı üzerindeki etkilerini araştırmayı amaçlamıştır.

Yöntemler: Çalışma, Aralık 2024-Mayıs 2025 tarihleri arasında Türkiye'nin güneydoğusunda yer alan bir kamu hastanesinde kesitsel ve karşılaştırmalı olarak yürütülmüştür. Gruplar servikal dilatasyon seviyelerine göre belirlenmiştir. Çalışmada, doğumhaneye kabul zamanına göre latent fazda (n=125) ve aktif fazda (n=125) olmak üzere iki gruba ayrılmış 250 gebeden oluşmuştur.

Bulgular: Çalışmada, mesane kateterizasyonu, oksijen desteği, epizyotomi ve sürekli fetal izleme gibi obstetrik müdahaleler, latent faz grubunda anlamlı olarak daha sık görüldü. Ancak, amniyotomi aktif faz grubunda anlamlı olarak daha sık görüldü. Yenidoğan sonuçları açısından gruplar arasında genel olarak anlamlı bir fark bulunmamakla birlikte (p>0,05), 5. dakika Apgar skorunun ve doğumdan sonraki ilk 30 dakika içinde emzirmeye başlama oranının aktif faz grubunda istatistiksel olarak anlamlı düzeyde daha yüksek olduğu saptanmıştır (p<0,05). Ayrıca, travmatik doğum algısı puanları latent faz grubunda, aktif faz grubuna kıyasla anlamlı düzeyde daha yüksek bulunmuştur (p<0,001).

Sonuç: Bu bulgular, doğumhaneye latent fazda kabul edilen kadınlarda amniyotomi dışındaki obstetrik müdahalelerin daha fazla uygulandığını ve bunun travmatik doğum algısını artırabileceğini göstermektedir.

Anahtar Kelimeler: Doğumhaneye kabul, ebelik, obstetrik girişimler, travma, yenidoğan

Address for Correspondence: Asst. Prof. Hatice Gül Öztaş, Kahramanmaraş Sütçü İmam University Faculty of Health Sciences, Department of Midwifery, Kahramanmaraş, Türkiye
E-mail: haticeguloztas@ksu.edu.tr
ORCID IDs of the authors: H.G.Ö.: 0000-0003-3574-2509, A.F.: 0009-0006-8316-3228

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Introduction

Labor is a physiological process in which cervical changes occur with regular uterine contractions and the fetus and its appendages are expelled from the uterus (1). Labor usually begins in the home environment, but women may be indecisive about determining the appropriate hospital admission time (2). The World Health Organization (WHO) recommends that women be admitted to the hospital when they reach the active labor phase after careful evaluation (3). However, in clinical practice, although admission to the delivery room is usually based on obstetric criteria, admission criteria are not clearly defined in many health institutions (4).

The labor process is generally examined in the literature in two phases: latent (early) and active (late). This biphasic classification is primarily based on cervical dilation dynamics, where the latent phase is characterized by gradual cervical effacement and slow dilation, whereas the active phase corresponds to an accelerated pattern of cervical change, a threshold that contemporary guidelines increasingly recognize at approximately 6 cm dilation rather than the historically accepted 4-5 cm benchmark (5,6). Admitting to the hospital in the early phase of labor may lead to a prolonged labor, more obstetric interventions, and an increase in cesarean section rates (7,8). Interventions performed in the latent phase mostly result in a diagnosis of dystocia; fetal distress comes to the fore in the active phase (9). Unnecessary obstetric interventions not only disrupt the natural physiological process of birth but can also negatively affect both maternal and neonatal outcomes (10). The WHO recommends that birth should be supported in its physiological flow as much as possible, and interventions should be applied only when medically necessary (3). However, the modern birth process often considers birth as a risky process and promotes early and routine interventions.

Childbirth is an important life experience for women that has not only physiological but also deep psychological effects. Factors such as inadequate support, prolonged labor, interventional practices, severe pain, and loss of control can cause childbirth to turn into a traumatic experience (11). The traumatic birth perception can result from various factors such as lack of health professional support, emergency cesarean section, interventional birth practices, intense labor pain, some routine obstetric interventions (electronic fetal monitoring, oxytocin infusion, fundal pressure, episiotomy, movement and feeding restriction), fear of childbirth, loss of control, prolonged labor, history of psychiatric illness, and high stress level (11,12). In the literature, it has been shown that the traumatic birth perception is significantly associated with weakening of mother-infant bonding, increased risk of postpartum depression, and increased likelihood of adverse maternal-fetal outcomes (2,13).

Studies that evaluate the holistic effects of delivery room admission time on the delivery process, neonatal outcomes, and traumatic birth perceptions are quite limited. Therefore, this study aims to comprehensively evaluate the effects of delivery room admission time on the delivery process, neonatal health, and women's traumatic birth perceptions.

Methods

Research Design, Location, and Time

This study was conducted with a comparative and cross-sectional design, and was conducted between December 2024 and May 2025 at the maternity ward of a public hospital in the southeast of Türkiye, with pregnant women who were admitted for vaginal delivery and met the pre-determined inclusion criteria.

Population/Sample of the Study

Sample size was calculated using the G*Power 3.1.7.4 program [Faul et al. (14)]. Based on an effect size of 0.30, a significance level of 0.05, and a statistical power of 90%, the minimum required sample size was determined as 107 participants for each group. Considering the possibility of data loss, the total sample size was increased to 250 participants. This sample size is consistent with previous studies investigating the effects of hospital admission timing on labor and neonatal outcomes (7), supporting the methodological adequacy of the present study.

Participants were recruited using a consecutive sampling method among eligible women admitted to the delivery unit during the study period. However, group allocation was not randomized; instead, participants were classified according to cervical dilatation at admission, in accordance with the clinical protocol applied in the study hospital and national obstetric guidelines (latent phase: ≤4 cm; active phase: ≥5 cm) (15).

Inclusion criteria were: being 18 years of age or older, having a singleton pregnancy, and being admitted to the delivery unit during the first stage of labor.

Data Collection

Before starting the study, the Ethics Committee decision was obtained from the University of Health Sciences Türkiye, Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (decision no: 79/2024, date: 20.11.2024). In the first stage, the data were collected by interviewing the pregnant women who were admitted to the hospital for delivery one-on-one in their rooms and filling out the "personal information form". This interview was conducted face-to-face and lasted 10-15 minutes on average. During the labor, the "labor follow-up form" was used to record the observations and interventions related to the labor process, and the "neonatal follow-up form

and Apgar form" were used to evaluate the health status of the newborn after birth. In the last stage of the study, the "traumatic birth perception scale (TBPS)" developed by Yalnız et al. (16) was applied to assess the level of perception of labor as a traumatic experience by the puerperal women 24 hours after birth. While the internal consistency coefficient (Cronbach's alpha) reported in the original study of the scale was 0.89, the Cronbach's alpha value of the scale in this study was calculated as 0.912. Informed consent was obtained from all participants after providing them with detailed information about the purpose, procedures, and confidentiality of the study, in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis of the data obtained in this study was performed using SPSS Statistics 30 software. First of all, normality distributions of variables were evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Similarities between variables were evaluated with the chi-square test, and differences between groups were evaluated with the Mann-Whitney U test. The findings were interpreted following the determined significance level ($p<0.05$).

Results

Table 1 presents the distribution of sociodemographic and obstetric characteristics of women by groups. It was determined that the groups were homogeneous in terms of age (p=0.108), gestational week (p=0.502), and delivery type (p=1.000). It was determined that the distribution of women in the groups was homogeneous in terms of educational level (p=0.796), employment (p=0.640), and income level (p=0.095). Statistically significant differences were found between the groups in terms of the number of live births (p<0.001), the number of living children (p<0.001), the number of pregnancies (p=0.001), pregnancy history (p<0.001), and receiving antenatal care (p=0.002).

Table 2 shows that there were significant differences between the groups in terms of cervical dilatation, fetal head level, amniotomy, continuous fetal monitoring, bladder catheterization, oxygen support, episiotomy, and manual removal of the placenta. No significant difference was observed regarding the need for neonatal intensive care. However, the 5th-minute Apgar score (p=0.015) and the time to first breastfeeding (p<0.001) differed significantly between the groups.

Table 3 presents the comparison of women's traumatic birth perception scores by groups. A statistically significant difference was found between the latent phase group [M=57, interquartile range (IQR)=50-63] and the active phase group (M=43, IQR=37-51) in terms of the mean scores of the TBPS (p<0.001). According to these results, the traumatic birth perception scores of women in the latent phase group were significantly higher than those of women in the active phase group.

Discussion

The study evaluated the effects of the timing of admission to the delivery room on the labor process, neonatal outcomes, and traumatic birth perceptions. The findings showed that the majority of women who were admitted to the delivery room in the active phase had previous birth experience, had a planned pregnancy, and received regular antenatal care. This suggests that birth experience improves women's ability to recognize signs of labor and manage the timing of admission to the hospital. Indeed, it

Table 1. Comparison of the sociodemographic and obstetric characteristics according to groups

Variables	Latent phase group n=125	Active phase group n=125	Total	Test & p-values
	M (IQR)	M (IQR)	M (IQR)	
Age	24 (21-27)	26 (22-27)	24 (21-27)	Z=1.607 p=0.108
Gestational week	39 (38-39)	38 (38-39)	39 (38-39)	Z=-0.672 p=0.502
Number of live births	0 (0-1)	1 (0-2)	1 (0-2)	**Z=3.895 p<0.001**
Number of living children	0 (0-1)	1 (0-2)	1 (0-2)	**Z=3.922 p<0.001**
Educational level				
Lower than high school	48 (38.4)	51 (40.8)	99 (39.6)	x^2=0.067
High school or higher	77 (61.6)	74 (59.2)	151 (60.4)	p=0.796
Employment				
Employed	24 (19.2)	28 (22.4)	52 (20.8)	x^2=0.219
Unemployed	101 (80.8)	97 (77.6)	198 (79.2)	p=0.640
Income level				
Low	66 (52.8)	80 (64.0)	146 (58.4)	x^2=2.783
Moderate/high	59 (47.2)	45 (36.0)	104 (41.6)	p=0.095
Number of pregnancies				
1	71 (56.8)	43 (34.4)	114 (45.6)	**x^2=11.755**
≥2	54 (43.2)	82 (65.6)	136 (54.4)	**p=0.001**
Pregnancy history				
Planned	92 (73.6)	116 (92.8)	208 (83.2)	**x^2=15.139**
Unplanned	33 (26.4)	9 (7.2)	42 (16.8)	**p<0.001**
Receiving antenatal care				
Present	87 (69.6)	108 (86.4)	195 (78.0)	**x^2=9.324**
Absent	38 (30.4)	17 (13.6)	55 (22.0)	**p=0.002**
Delivery type				
Caesarean	6 (4.8)	5 (4.0)	11 (4.4)	x^2=0.000
Vaginal	119 (95.2)	120 (96.0)	239 (95.6)	p=1.000

M (IQR): Median (25th and 75th percentiles), IQR: Interquartile range, n: Number, %: Percentage, Z: Mann-Whitney U test standardized Z test value, x^2: Chi-square test

Table 2. Comparison of the birth process and neonatal characteristics according to groups

Variables	Latent phase group n=125	Active phase group n=125	Total	Test & p-values
	M (IQR)	M (IQR)	M (IQR)	
Cervical dilatation (cm)	2 (1-3)	6 (5-8)	4 (2-6)	**Z=13.803** **p<0.001**
Reasons for coming to the delivery room				
Presence of contraction	95 (76.0)	91 (72.8)	186 (74.4)	x^2=5.354 p=0.069
Rupture of membranes	17 (13.6)	28 (22.4)	45 (18.0)	
Contraction + membrane rupture	13 (10.4)	6 (4.8)	19 (7.6)	
Level of the fetal head				
-3	71 (56.8)	19 (15.2)	90 (36.0)	**x^2=77.336** **p<0.001**
-2	47 (37.6)	41 (32.8)	88 (35.2)	
-1 or 0	7 (5.6)	61 (48.8)	68 (27.2)	
+1 or +2	0 (0.0)	4 (3.2)	4 (1.6)	
Amniotomy				
Present	35 (28.0)	70 (56.0)	105 (42.0)	**x^2=18.982** **p<0.001**
Absent	90 (72.0)	55 (44.0)	145 (58.0)	
Continuous fetal monitoring				
Present	20 (16.0)	9 (7.2)	29 (11.6)	**x^2=3.901** **p=0.048**
Absent	105 (84.0)	116 (92.8)	221 (88.4)	
Bladder catheterization				
Present	124 (99.2)	87 (69.6)	211 (84.4)	**x^2=39.373**
Absent	1 (0.8)	38 (30.4)	39 (15.6)	p<0.001
Oxygen support in labor				
Present	44 (35.2)	10 (8.0)	54 (21.6)	**x^2=25.723**
Absent	81 (64.8)	115 (92.0)	196 (78.4)	p<0.001
Episiotomy				
Present	80 (64.0)	48 (38.4)	128 (51.2)	**x^2=15.385**
Absent	45 (36.0)	77 (61.6)	122 (48.8)	**p<0.001**
Manual removal of the placenta				
Present	22 (17.6)	6 (4.8)	28 (11.2)	**x^2=9.049**
Absent	103 (82.4)	119 (95.2)	222 (88.8)	**p=0.003**
5th-minute Apgar	10 (9-10)	10 (10-10)	10 (10-10)	**Z=2.427** **p=0.015**
Neonatal intensive care requirement				
Present	5 (4.0)	2 (1.6)	7 (2.8)	-
Absent	120 (96.0)	123 (98.4)	243 (97.2)	p=0.446*
First breastfeeding time				
No breastfeeding	5 (4.0)	1 (0.8)	6 (2.4)	**x^2=18.700** **p<0.001**
In first 30 minutes	54 (43.2)	87 (69.6)	141 (56.4)	
Between 30-60 minutes	62 (49.6)	34 (27.2)	96 (38.4)	
After 60 minutes	4 (3.2)	3 (2.4)	7 (2.8)	

M (IQR): Median (25th and 75th percentiles), IQR: Interquartile range, n: Number, %: Percentage, Z: Mann-Whitney U test standardized Z test value, x^2: Chi-square test, *: Fisher's exact test, NA: Not analyzed

is stated in the literature that women who will have their first birth tend to admit to the hospital in the early stages of labor (2,13). It is stated that women who attend regular pregnancy check-ups are more conscious about which stage of labor they should admit at (17,18).

When obstetric interventions were evaluated, women admitted to the delivery room during the latent phase were exposed to more interventions such as bladder catheterization, oxygen support, continuous fetal monitoring, episiotomy, and manual removal of the placenta. These findings suggest that initiating labor management before the onset of the active phase may increase the likelihood of medical interventions during childbirth. Similar results have been reported in the literature, indicating that admission during the latent phase is associated with higher rates of obstetric interventions and a greater likelihood of medicalized labor management (19-21). However, in the present study, amniotomy was performed more frequently in the active phase group. This finding may be explained by the clinical practice of performing amniotomy after the active phase of labor has been established in order to accelerate labor progress (3,22). Consistent with our results, Karakoç et al. (22) also reported that the rate of amniotomy was higher among women admitted during the active phase of labor. The authors suggested that amniotomy is often applied during the later stages of labor to facilitate cervical dilation and shorten the duration of the second stage. Therefore, allowing labor to progress physiologically until the active phase may contribute to reducing unnecessary

Table 3. Comparison of the women's traumatic birth perception scores by groups

Scale	Latent phase group n=125		Active phase group n=125				
TBPS	M (IQR)	MR	M (IQR)	MR	U	Z	p
	57 (50-63)	166.65	43 (37-51)	84.35	**2668.50**	**-9.002**	**p<0.001**

MR: Mean rank, M (IQR): Median (25th and 75th percentiles), IQR: Interquartile range, Z: Mann Whitney U test standardized Z test value, TBPS: Traumatic birth perception scale

obstetric interventions while supporting a more natural birth process.

In terms of neonatal outcomes, it was found that babies in the active phase group had higher 5th-minute Apgar scores and shorter breastfeeding initiation times. This finding might be a result of the shorter delivery time with admission in the active phase, less physical and psychological wear on the mother, and less intervention. However, some studies have reported that the time of admission to the delivery room does not have a significant effect on Apgar scores (2,7). It is thought that these differences may be due to differences in sample structures and birth protocols. The earlier initiation of breastfeeding by women in the active phase group after birth is a positive situation in terms of both colostrum intake and mother-baby bonding (20,23). It is stated in the literature that early breastfeeding is affected by many factors such as the duration of labor, type of delivery, interventions applied, birth environment, and complications (18,24). Interventions and prolongation of labor may cause fatigue in the mother and newborn and delay the breastfeeding period (25).

Since birth is not only a physiological but also a psychological process, one of the most striking findings of the study is the perception of traumatic birth. The traumatic birth perception scores of women admitted to the delivery room in the latent phase were found to be significantly higher compared to the active phase group. This result shows that women who were admitted to the hospital in the early phase of labor perceive the process as a more negative experience due to being exposed to more interventions, the duration of labor being prolonged, and losing the sense of control. It was also stated in the literature that factors such as loss of control, severe pain, excessive interventions, and insufficient social support increase traumatic birth perceptions (26-28). A traumatic birth experience is a significant factor affecting women's psychological well-being not only during childbirth but also in the postnatal period. Research shows that the perception of a traumatic birth is significantly associated with postnatal depression, anxiety disorders, postnatal post-traumatic stress disorder and mother-infant bonding problems (3,29-31). In particular, the feeling of emotional detachment that develops after trauma can reduce the mother's capacity to provide care and negatively affect the baby's development. Therefore, preventing traumatic experiences during the birth process is critical not only in the short term but also in terms of long-term psychosocial outcomes (3). In this context, managing the birth process following the principles of woman-centered, respectful, and individualized care strengthens the role of midwifery care in both supporting physiological birth and preventing traumatic experiences.

Study Limitations

This study has several limitations that should be considered when interpreting the findings. First, the research was conducted in a single public hospital in southeastern Türkiye, which may limit the generalizability of the findings to other regions or healthcare settings. Second, the cross-sectional and observational design of the study did not allow causal inference between the timing of admission to the delivery room and the outcomes observed. Additionally, the use of self-report-based measures, such as the TBPS, may introduce recall or response bias, as these were administered within the first 24 hours postpartum. Moreover, the study did not evaluate long-term maternal or neonatal outcomes, limiting the ability to assess the broader impact of delivery room admission timing on health and well-being. Another important limitation was the disproportionate number of multiparous women in the active phase group. Since multiparity is associated with shorter labour duration and potentially more positive birth experiences, this difference may have influenced participants' traumatic birth perception scores. Future research should aim to control for parity when comparing birth experiences. Finally, the criterion used to define the active phase of labour represents a methodological limitation. Although recent international guidelines increasingly define the onset of the active phase at approximately 6 cm cervical dilatation, this study used a ≥5 cm threshold according to the clinical protocol applied in the study hospital during the data collection period. Therefore, this methodological difference should be considered when interpreting the findings and comparing the results with studies that use the 6 cm criterion to define the onset of active labour.

Conclusion

The study revealed the effects of the timing of admission to the delivery room on the delivery process, neonatal health, and traumatic birth perceptions. It was determined that women who were admitted in the active phase had better neonatal outcomes, a shorter time to breastfeed, and lower traumatic birth perceptions. In contrast, those

who were admitted in the latent phase had more obstetric interventions and higher traumatic birth perceptions. The findings emphasize the importance of admission to the delivery room in the active phase and women-centered care. It was also stated that raising awareness of the correct timing of admission through antenatal training could provide positive effects.

Ethics

Ethics Committee Approval: Ethics Committee Decision was obtained from the University of Health Sciences Türkiye, Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (decision no: 79/2024, date: 20.11.2024).

Informed Consent: Informed consent was obtained from all participants after providing them with detailed information about the purpose, procedures, and confidentiality of the study, in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G.Ö., A.F., Concept: H.G.Ö., A.F., Design: H.G.Ö., A.F., Data Collection or Processing: H.G.Ö., A.F., Analysis or Interpretation: H.G.Ö., A.F., Literature Search: H.G.Ö., A.F., Writing: H.G.Ö.

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Original Article

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The Diagnostic Value of Combined Hip and Systemic Ultrasonography for the Early Detection of Developmental Dysplasia of the Hip and Associated Pathologies in Infants

Bebeklerde Gelişimsel Kalça Displazisi ve Eşlik Eden Patolojilerin Erken Tanısında Kombine Kalça ve Sistemik Ultrasonografinin Tanısal Değeri

Korcan Aysun GÖNEN[1], Nevin CAMBAZ KURT[2], Özlem Mehtap BOSTAN[3]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Türkiye
[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Pediatrics, İstanbul, Türkiye
[3]Bursa Uludağ University Faculty of Medicine, Department of Pediatrics, Bursa, Türkiye

ABSTRACT

Objective: To assess the diagnostic value of combined hip and systemic ultrasonography in infants for the early detection of developmental dysplasia of the hip (DDH) and other incidental pathologies.

Methods: A retrospective chart review was conducted for infants who underwent both hip and systemic sonographic examinations. The infants were categorized into two groups: group 1 (normal) and group 2 (with DDH). Data analysis included risk factors associated with DDH, hip type, and systemic sonographic findings.

Results: Among the 496 hips scanned, 336 (67.7%) were classified as normal (group 1), and 160 (32.3%) were diagnosed with DDH (group 2). The hip types in group 2 included 2a in 75 patients (15%), 2b in 58 patients (11.7%), 2c in 18 patients (3.6%), 3 in 7 patients (1.4%), and 4 in 2 patients (0.4%). A total of 63 (25%) incidental pathologies were detected, with 35 (14%) involving the head and neck and 26 (10.5%) involving the abdomen. While most risk factors did not significantly differ between the groups, sex (p=0.004) and a family history of DDH (p<0.001) were identified as significant predictors.

Conclusion: Comprehensive ultrasonographic examination of the hips and other organ systems in infants can be valuable

ÖZ

Amaç: Kombine kalça ve sistemik ultrasonografinin, bebeklerde gelişimsel kalça displazisi (GKD) ve diğer tesadüfi patolojilerin erken tespitindeki tanısal değerini değerlendirmek.

Yöntemler: Kalça ve sistemik sonografi incelemeleri yapılan bebekler için retrospektif bir dosya taraması gerçekleştirildi. Bebekler iki gruba ayrıldı: grup 1 (normal) ve grup 2 (GKD olan). Veri analizi, GKD ile ilişkili risk faktörlerini, kalça tiplerini ve sistemik sonografi bulgularını içermektedir.

Bulgular: Taranan 496 kalçadan 336'sı (%67,7) normal (grup 1) olarak sınıflandırıldı, Hastaların 160'ı (%32,3) GKD tanısı aldı (grup 2). Grup 2'deki kalça tiplerinden 2a 75 hastada (%15), 2b 58 hastada (%11,7), 2c 18 hastada (%3,6), 3 ise 7 hastada (%1,4) ve 4, 2 hastada (%0,4) saptandı. Toplamda 63 (%25) hastada tesadüfi patoloji tespit edildi; bunlardan 35'i (%14) baş ve boyun, 26'sı (%10,5) ise karın ile ilgiliydi. Çoğu risk faktörü gruplar arasında anlamlı bir fark göstermemekle birlikte, cinsiyet (p=0,004) ve ailede GKD olması öyküsü (p<0,001) önemli belirleyiciler olarak saptanmıştır.

Sonuç: Bebeklerde kalça ve diğer organ sistemlerinin kapsamlı ultrasonografik muayenesi, GKD ve diğer tesadüfi bulgular da dahil olmak üzere patolojilerin erken tespiti için değerli bir araç olabilir.

Address for Correspondence: Assoc. Prof., Korcan Aysun Gönen, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Türkiye
E-mail: aysunbalc@yahoo.com
ORCID IDs of the authors: K.A.G.: 0000-0003-4731-7972, N.C.K.: 0000-0003-4066-1834, Ö.M.B.: 0000-0001-7707-2174

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ABSTRACT

tools for the early detection of pathologies, including DDH, and other incidental findings.

Keywords: Developmental dysplasia of the hip, infant, ultrasonography, retrospective studies, incidental findings

ÖZ

Anahtar Kelimeler: Kalça gelişimsel displazisi, bebek, ultrasonografi, retrospektif çalışmalar, tesadüfi bulgular

Introduction

Developmental dysplasia of the hip (DDH) is a common orthopedic condition in children, and screening practices vary across regions due to differing local healthcare policies. Early diagnosis is crucial for preventing morbidity and potential sequelae in DDH (1). One of the most common anomalies associated with DDH is torticollis, with an incidence in newborns ranging between 0.017% and 1.9% (2). Ultrasonography (US) is routinely used in many centers for the diagnosis of both DDH and torticollis. Similarly, neonatal sonographic screening of various systems has become an integral part of public health screening programs in certain institutionalized populations. In recent years, prenatal and postnatal ultrasound screening for renal and urinary tract anomalies has also been widely implemented (3-5). Although its effectiveness remains controversial, postnatal US has been shown to be more reliable in diagnosing urinary system anomalies than prenatal screening is (5).

Cranial US is another imaging method increasingly used in newborns, particularly in premature infants, and has become a standard practice in neonatal intensive care units. While cranial US has traditionally been indicated for infants with neurological symptoms, recent studies highlight the potential benefits of cranial US screening in asymptomatic healthy newborns and full-term infants, which is noteworthy (6,7).

In our study, we examined additional sonographic findings and explored the necessity of routine systemic sonographic screening in healthy infants undergoing routine hip US in radiology.

Methods

We retrospectively analyzed the medical records of infants referred from different hospitals for routine hip US screening between 2012 and 2020. Infants aged 1-6 months were included in the study. Infants who did not undergo a comprehensive US examination of all systems were excluded. Detailed anamnesis was taken from each patient, including demographic data such as age, sex, birth order, type of delivery (normal/cesarean), breech presentation, foot anomalies, family history of DDH, and prenatal second-level obstetric US information. Physical examinations were performed for possible foot deformities in each infant. Patients without detailed demographic or medical information were excluded, resulting in a total of 248 infants included in the study. The fasting times of the patients prior to the examination were recorded.

US examinations were performed while the infants were asleep whenever possible. Hip US was conducted via the Graf method in the right and left lateral decubitus positions. Additional US evaluations included the neck (for torticollis, thyroid, and thymus), fontanel, abdomen, and umbilical, inguinal, and scrotal regions. Sternocleidomastoid muscle diameters were measured in the sagittal plane with the infant in the supine position, and echogenicity was assessed for signs of torticollis. The thyroid gland was scanned for nodules in both the axial and sagittal planes. The cardiac region was examined with the abdominal probe angled superiorly while the infant was in the supine position. The umbilical and inguinal regions were evaluated for hernias, whereas the ovaries in female infants and the scrotal region in male infants were examined.

The average time for each US examination was 30 minutes per infant. All US scans were performed by the same radiologist (KAG) via an Aplio XG US scanner (Toshiba Medical Systems, 2011, Japan) equipped with multifrequency transducers (a 3.5 MHz convex probe for abdominal scanning; a 5 MHz microconvex probe for transfontanel scans; and a 7.5 MHz superficial probe for the neck, hip, and scrotum).

This study was approved by the local Ethics Committee of Tekirdağ Namık Kemal University (protocol no: 2022.33.03.01, date: 29.03.2022) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all parents.

Statistical Analysis

Statistical analysis was performed via SPSS for Windows version 22.0 (Statistical Product and Service Solutions, Inc, Chicago, IL, USA). The descriptive data are presented as the means ± standard errors. Differences between groups were assessed via Pearson chi-square tests and independent-sample t-tests. A p-value of <0.05 was considered statistically significant.

Results

A total of 248 infants, 133 girls (53.6%) and 115 boys (46.4%), participated in the study. The mean age was 97.7±40.7 days

(range: 30-183 days). Among the participants, 25 infants (10%) were under 6 weeks of age, whereas 223 infants (90%) were older than 6 weeks. There were 95 infants (38.3%) aged between 6 weeks and 3 months. None of the infants had a documented history of second-level obstetric ultrasound during the prenatal period. The performance of Ortolani or Barlow tests as part of the physical examination was unknown, and no documentation regarding these tests was available in the ultrasound request forms. The fasting times prior to ultrasound varied from 0 to 4 hours (mean: 2.0±0.9 hours).

The infants were categorized into two groups: the normal group (n=142; 57.3%) and the DDH group (n=106; 42.7%). Among the 106 patients in the DDH group, 53 (50%) had bilateral DDH, 48 (45%) had left-sided DDH, and 5 (5%) had right-sided DDH. Detailed demographic findings, along with clinical and sonographic data (including sex, risk factors, DDH types, and affected sides), are summarized in Table 1.

Significant differences were observed between the DDH group and the normal group in terms of sex and family history of DDH (p=0.004 and p<0.001, respectively). However, no statistically significant differences in other risk factors were detected between the two groups.

Among the 496 hips scanned, 336 (67.7%) were classified as normal (group 1), and 160 (32.3%) were classified as DDH (group 2). The hip types in group 2 included 2a in 75 patients (15%), 2b in 58 patients (11.7%), 2c in 18 patients (3.6%), type 3 in 7 patients (1.4%), and type 4 in 2 patients (0.4%) (Table 1). Isolated left-sided DDH was identified in 2 patients with right-sided torticollis and in 7 patients with left-sided torticollis. Notably, isolated right-sided DDH was not observed in any patients with torticollis. Bilateral DDH was present in 2 patients with right-sided torticollis and in 3 patients with left-sided torticollis. In 12 out of 14 patients with both torticollis and DDH, the torticollis was on the ipsilateral side.

No statistically significant differences in sonographic hip types were observed between different age groups (p=0.152).

The distribution of pathologies identified through systemic ultrasonographic analysis is summarized in Table 2. Of these, 35 pathologies (14%) were related to the head/neck, and 26 (10.5%) were related to the abdomen. A majority (34.6%) of the abdominal pathologies were associated with the kidneys. Abnormalities in the size and shape of the heart chambers were noted in 2 patients (0.8%) exhibiting growth retardation, leading to a diagnosis of congenital heart disease in these patients following consultation with a pediatric cardiologist.

The incidence of accompanying anomalies was significantly higher in patients without a family history of DDH compared to those with a positive family history, and this difference was statistically significant.

Discussion

Neonatal sonographic screening is a vital tool for detecting conditions, including DDH, that necessitate early intervention in newborns and infants (2). Numerous studies underscore its significance (1-5). Although DDH is relatively uncommon, hip ultrasound screening is widely integrated into public health programs across many countries (8,9). However, the implementation of additional neonatal sonographic screening programs remains limited.

In this study, DDH was diagnosed in 32.3% of infants undergoing routine hip US. Additionally, a substantial number of other pathologies were detected, with 63 cases (25%) identified through ultrasound examinations of various organ systems. Specifically, 35 (14%) of these pathologies involved the head and neck, while 26 (10.5%) were related to abdominal conditions.

Table 1. Patient demographic findings, possible risk factors for DDH, DDH types and sides, and additional US findings

Parameters		Groups		p-value
		Normal	DDH	
Gender, n (%)	Female	65 (45.8%)	68 (64.2%)	**0.004***
	Male	77 (54.2%)	38 (35.8%)	
Birth order, n (%)	1st	79 (55.6%)	68 (64.2%)	0.177
	>1st	63 (44.4%)	38 (35.8%)	
DDH history, n (%)	Yes	3 (2.1%)	15 (14.2%)	**0.001***
	No	139 (97.9%)	91 (85.8%)	
Type of birth, n (%)	Normal	75 (52.8%)	53 (50%)	0.661
	Cesarean	67 (47.2%)	53 (50%)	
Birth presentation, n (%)	Head	74 (98.7%)	52 (98.1%)	1.000
	Breech	1 (1.3%)	1 (1.9%)	
Foot anomaly, n (%)	Yes	2 (1.4%)	0 (0)	0.509
	No	140 (98.6%)	106 (100%)	
Torticollis, n (%)	Yes	9 (6.3%)	14 (13.2%)	0.065
	No	133 (93.7%)	92 (86.8%)	
Torticollis side, n (%)	Right	4 (44.4%)	4 (28.6%)	0.657
	Left	5 (55.6%)	10 (71.4%)	
DDH type, n (%)	1	336 (67.7%)		
	2a		75 (15.1%)	
	2b		58 (11.7%)	
	2c		18 (3.6%)	
	3		7 (1.4%)	
	4		2 (0.4%)	
DDH side, n (%)	Right		59 (36.9%)	
	Left		101 (63.1%)	
Additional US pathology, n (%)	Yes	30 (21.1)	10 (9.4)	0.091
	No	112 (78.9)	96 (90.6)	

*: Chi-square test, DDH: Developmental dysplasia of the hip, US: Ultrasonography

A review of the literature identified a single study involving 769 infants, which reported a 28% incidence of incidental anomalies detected via abdominal ultrasound in infants aged 0 to 1 year (10). Furthermore, a retrospective analysis of 11,681 healthy newborns found cranial anomalies in 17.3% of cases (6). The rates of hip dislocation, renal pathology, and brain anomalies in a cohort of 3,396 healthy newborns were reported to be 17.1%, 4.4%, and 4.2%, respectively (11). In our study, the majority of detected pathologies were found in infants without DDH, and no statistically significant differences were observed between the groups.

Among the 24 patients presenting with accompanying anomalies, 8 demonstrated type 2a morphology, 8 exhibited type 2b, and 8 showed type 2c morphology.

Table 2. Additional systemic pathologies detected via ultrasonography

Ultrasonographic pathologies	Groups		
	Normal (n=142)	DDH (n=106)	Total (n=248)
Torticollis, n (%)	9 (6.3%)	14 (13.2%)	23 (9.3%)
Kidney stone, n (%)	2 (1.4%)	1 (0.9%)	3 (1.2%)
Hydronephrosis, n (%)	4 (2.8%)		4 (1.6%)
Ectopic kidney, n (%)	1 (0.7%)	1 (0.9%)	2 (0.8%)
Umbilical hernia, n (%)	4 (2.8%)	2 (1.9%)	6 (2.4%)
Inguinal hernia, n (%)	3 (2.1%)		3 (1.2%)
Hepatosplenomegaly, n (%)	2 (1.4%)		2 (0.8%)
Ovarian cyst, n (%)		3 (2.8%)	3 (1.2%)
Epididymis cyst, n (%)		1 (0.9%)	1 (0.4%)
Undescended testis, n (%)		1 (0.9%)	1 (0.4%)
Situs inversus, n (%)		1 (0.9%)	1 (0.4%)
Congenital heart disease, n (%)	2 (1.4%)		2 (0.8%)
Hydrocephalus, n (%)	4 (2.8%)		4 (1.6%)
Septum pellucidum et vergae variation, n (%)	2 (1.4%)		2 (0.8%)
Thyroid nodule, n (%)	5 (3.5%)		5 (2%)
Thyroid hypoplasia, n (%)	1 (0.7%)		1 (0.4%)
Total, n (%)	39 (27.3%)	24 (22.6%)	63 (25%)

DDH: Developmental dysplasia of the hip

DDH is influenced by a combination of genetic, environmental, and biomechanical factors. Key risk factors include a positive family history of the condition, breech presentation, female sex, firstborn status, and associated conditions such as torticollis. Furthermore, factors like ligamentous laxity, prenatal positioning, and swaddling practices may also contribute to the development of DDH (12-15).

In our study, there were no statistically significant differences in risk factors between the groups, except for sex and family history of DDH. The higher prevalence of DDH in girls aligns with the literature (12,16).

The most commonly recognized congenital anomalies associated with DDH are foot deformities, such as pes equinovarus and pes calcaneovalgus (2,14,15). Additionally, rare congenital anomalies have been documented, with congenital hypothyroidism being the most common (17).

In our study, two patients presented with foot anomalies, two with congenital heart defects, and one with thyroid hypoplasia; all of these cases were categorized within the normal hip morphology group. A 30-day-old female infant with situs inversus exhibited bilateral type 2a hip morphology, which was most likely attributable to her early age. Nonetheless, DDH may also be associated with conditions such as cerebral palsy-affecting in utero extremity positioning due to muscular weakness-and Joubert syndrome, which is characterized by congenital cerebellar ataxia, hypotonia, oculomotor apraxia, cystic kidney disease, and hepatic fibrosis (18,19).

Delayed diagnosis of DDH can lead to serious complications, including delays in walking, asymmetrical leg length, chronic pain, avascular necrosis, and osteoarthritis, which may ultimately necessitate total hip replacement (1). During the neonatal period, DDH can be identified through Ortolani and Barlow tests during physical examinations; however, limited abduction is considered the most reliable physical finding in this age group (12). In our cases, none of these tests or findings were recorded. Given the lack of significant correlations between pathological physical examination findings and DDH, routine sonographic screening is recommended for DDH even in the presence of normal physical examination results (12).

Ultrasound is recognized as the most sensitive method for diagnosing DDH (1,2). According to the literature, the incidence of DDH identified via ultrasound ranges from 0.8 % to 30% (12,14,19-22). The incidence of DDH in our study was found to be relatively high at 32.3% compared to rates reported in the literature. This elevated rate may be attributed to the limited sample size, which can amplify the influence of outliers on prevalence estimates, as well as selection bias arising from the inclusion of some infants who underwent systemic US due to clinical suspicion, potentially leading to an overestimation of DDH prevalence.

Although opinions vary regarding the optimal timing for hip ultrasound, the sixth week is often cited as a period when minor temporary abnormalities resolve and more permanent anomalies can be identified (12). A study reported that clinical stabilization of the hip occurred without treatment by 4-6 weeks of age in 19 out of 30 infants (63%) (23). In our cohort, 23 hips (46%) among the 25 patients under 6 weeks of age were classified as type 2a, whereas 3 hips (6%) were classified as type 2c. Our total number of type 2a hips was 52 (27.4%) in infants aged 6 weeks to 3 months; however, we did not find a statistically significant difference in hip type between the two age groups.

The most prevalent pathology identified in the head and neck region was torticollis, whereas cranial anomalies were the least common. The co-occurrence of torticollis and DDH has been reported to range from 0% to 29% (2,24-26). Some authors argue that the history and physical examination findings are sufficient for diagnosing DDH in infants with torticollis, rendering routine hip ultrasound unnecessary (2). Typically, torticollis is detected on the same side as DDH (2,14,25). In our study, there were no statistically significant differences in torticollis incidence between the groups; however, ipsilateral torticollis was observed in 12 of the 14 patients with both torticollis and DDH in our DDH group. Ultrasound is an important diagnostic tool for torticollis, just as it is for DDH (27).

US plays a crucial role in the early detection of intracranial anomalies in healthy newborns (7,28). In a study of 11,681 healthy full-term newborns, the incidence of intracranial anomalies was found to be 17.3%, with approximately 5.7% of these infants developing neurodevelopmental disorders at follow-up (6). Notably, we did not observe any significant cranial pathology aside from hydrocephalus.

For newborn infants, abdominal US examination is recommended as a screening tool, particularly for the urinary system, in conjunction with hip assessments (3,5,11). Renal tract malformations are a leading cause of childhood end-stage renal disease, and chronic kidney disease can lead to both kidney failure and an increased risk of cardiovascular disease (4).

The prevalence of congenital kidney and urinary tract anomalies detected via antenatal US is approximately 0.1%, increasing to 1% with postnatal US (4). In a screening study involving 17,783 healthy infants, congenital urinary tract anomalies were identified in 171 patients, 42 of whom underwent surgical intervention. Additionally, several serious extrarenal intra-abdominal pathologies have been detected (5). The most common finding in abdominal US scans is hydronephrosis, with ureteropelvic obstruction being the most frequent congenital anomaly associated with it (4). Hydronephrosis presenting with a renal pelvis diameter of 5-20 mm or a grade 1-2 ratio during the fetal or neonatal period may undergo spontaneous resolution (3,29). In this study, the predominant abdominal pathologies related to the kidneys included hydronephrosis, renal calculi, and ectopic kidneys. A correlation between nephrolithiasis detected in the first year of life and metabolic abnormalities has been reported (30). Urolithiasis in newborns and infants may resolve spontaneously within the first year, whereas hydronephrosis may resolve by the second year (31). However, spontaneous resolution did not occur in the follow-up of our three patients with renal calculi. Ovarian cysts are more prevalent than expected during the neonatal period, with an incidence of 30% (3). Cysts exceeding 4 cm are considered pathological; in our cases, none exceeded this size.

Major congenital anomalies affect 2.3% to 4.1% of live births, making it essential to thoroughly investigate for additional anomalies when any congenital anomaly is detected in a newborn (32). A large study on the prevalence of congenital renal anomalies found that screening policies significantly influence outcomes, with the lowest detection rates in countries without routine ultrasound screening (33).

In our study, sonographic anomalies were detected in 63 out of 248 infants who were referred for screening and considered healthy. This corresponds to a rate of approximately 25%, and the majority of these pathologies are of a clinically significant nature.

In our country, routine hip examinations during the neonatal period are recommended to identify high-risk and clinically suspicious groups, facilitating early and appropriate treatment (34). However, aside from hip ultrasound scans, there are currently no studies or recommendations for routine systemic sonographic screening of specific organ systems during infancy. As this study highlights, not all infants undergo prenatal ultrasound screening, and even when performed, the effectiveness of this screening as a second-level review is limited by high costs and a shortage of qualified professionals.

Study Limitations

This study has several limitations. First, it had a retrospective design, and the data were obtained from cases in which both hip US and systemic US were performed during the same session. Systemic US was conducted in some patients as part of routine clinical protocols, at the discretion of the physician, or for the evaluation of additional anomalies. However, due to the retrospective nature of the study, the specific indications for performing systemic US could not be consistently documented. This should be taken into account when interpreting the results.

Second, the relatively small sample size might limit the generalizability of the findings. Performing a comprehensive ultrasonographic examination-including hip, cranial, cervical, abdominal, and scrotal imaging-in a single session is both time-consuming and labor-intensive.

To our knowledge, no previous studies in the literature have routinely performed systemic US alongside hip US as done in this study. This lack of standardization hinders the comparison of physical examination findings with ultrasonographic results and limits the ability to uniformly assess the indications for systemic imaging.

Conclusion

This study underscores the critical role of US as an effective screening tool for the early detection of systemic pathologies in infants. The findings reveal a significant prevalence of intracranial anomalies and renal tract malformations in otherwise healthy newborns, emphasizing the necessity of routine abdominal and cranial US examinations in conjunction with hip assessments. Given its non-invasive nature, accessibility, and cost-effectiveness -particularly its avoidance of X-ray exposure- there is a compelling justification for the broader application of US in the early identification of potentially preventable conditions. Although statistical significance was not achieved in all cases, the evidence suggests that comprehensive screening encompassing multiple organ systems during routine evaluations may substantially enhance the timely identification and management of potential health issues in infants, ultimately improving long-term health outcomes. The opportunity to rapidly screen other systems in all infants undergoing hip ultrasound-regardless of the primary reason for referral-is considered highly valuable, especially given the challenging conditions in our outpatient clinics.

Ethics

Ethics Committee Approval: This study was approved by the local Ethics Committee of Tekirdağ Namık Kemal University (protocol no: 2022.33.03.01, date: 29.03.2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all parents.

Footnotes

Authorship Contributions

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

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Original Article

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The Value of Radiographic Parameters to Predict Loss of Reduction in the Conservative Treatment of Distal Radius Fractures

Distal Radius Kırıklarının Konservatif Tedavisinde Redüksiyon Kaybını Tahmin Etmede Radyografik Parametrelerin Değeri

Halit CENGİZ[1], Ali UTKAN[2], Bülent ÖZKURT[2]

[1]University of Health Sciences Türkiye, Ankara Atatürk Sanatory Education and Research Hospital, Clinic of Orthopedics and Traumatology, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Ankara City Hospital, Department of Orthopedics and Traumatology, Ankara, Türkiye

ABSTRACT

Objective: Distal radius fractures are the most common fractures of the upper extremity. The aims of this study were to determine the radiologic parameters that could predict maintenance of reduction during conservative treatment of distal radius fractures and to present the functional outcomes at 6th month of treatment in individuals with and without loss of reduction.

Methods: A total of 146 individuals that were treated conservatively (reduction and casting) were included. Radiographic parameters including radial inclination, radial height, articular step-off, three-point index (TPI), cast index, and padding index were examined. The clinical outcomes were assessed at the 6th month of reduction by visual analog scale (VAS), QuickDASH and Mayo wrist score. Logistic regression analysis was performed to determine the predictive value of radiographic parameters in loss of reduction.

Results: The mean age was 40.17±13.30. Loss of reduction was detected in 21.2%. Significant differences were found in the articular step-off, TPI and cast indices between individuals with and without loss of reduction ($p<0.05$). TPI and cast index were found to be highly predictive for loss of reduction in fractures with and without extension to the distal radius joint,

ÖZ

Amaç: Distal radius kırıkları üst ekstremitenin en sık görülen kırıklarıdır. Bu çalışmanın amacı, distal radius kırıklarının konservatif tedavisi sırasında redüksiyonun sürdürülmesini öngörebilen radyolojik parametreleri belirlemek ve redüksiyon kaybı olan ve olmayan bireylerde tedavinin 6. ayındaki fonksiyonel sonuçları sunmaktır.

Yöntemler: Konservatif olarak tedavi edilen (redüksiyon ve alçı) toplam 146 birey dahil edildi. Radyal inklinasyon, radyal yükseklik, eklem içi basamaklanma, üç nokta indeksi (TPI), cast indeksi ve padding indeksi gibi radyografik parametreler incelendi. Klinik sonuçlar, redüksiyonun 6. ayında görsel analog skala (VAS), QuickDASH ve Mayo bilek skoru ile değerlendirildi. Radyografik parametrelerin redüksiyon kaybındaki öngörücü değerini belirlemek için lojistik regresyon analizi yapıldı.

Bulgular: Ortalama yaş 40,17±13,30 idi. Redüksiyon kaybı %21,2'sinde tespit edildi. Redüksiyon kaybı olan ve olmayan bireyler arasında eklem içi basamaklanma, TPI ve cast indekslerinde anlamlı farklılıklar bulundu ($p<0,05$). TPI ve cast indeksinin sırasıyla distal radius eklemine ekstansiyonu olan ve olmayan kırıklarda redüksiyon kaybı için yüksek öngörücü olduğu bulundu. Redüksiyon kaybı olan ve olmayan bireyler arasında VAS dışında fonksiyonel parametrelerde fark yoktu ($p>0,05$).

Address for Correspondence: Halit Cengiz MD, University of Health Sciences Türkiye, Ankara Atatürk Sanatory Education and Research Hospital, Clinic of Orthopedics and Traumatology, Ankara, Türkiye
E-mail: drhalitcengiz@windowslive.com
ORCID IDs of the authors: H.C.: 0000-0002-1121-9599, A.U.: 0000-0002-3653-3998, B.Ö.: 0000-0002-6135-1870.

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ABSTRACT

respectively. There was no difference in functional parameters other than VAS between individuals with and without loss of reduction (p>0.05).

Conclusion: Among the radiographic measures, TPI and cast indexes were the ones which had the higher predictive value for loss of reduction during conservative treatment in distal radius fractures.

Keywords: Conservative treatment, closed fracture reduction, distal radius fracture, plaster cast

ÖZ

Sonuç: Radyografik ölçümler arasında TPI ve cast indeksleri, distal radius kırıklarında konservatif tedavi sırasında redüksiyon kaybı için en yüksek öngörücü değere sahip olanlardı.

Anahtar Kelimeler: Konservatif tedavi, kapalı kırık redüksiyonu, distal radius kırığı, alçı

Introduction

Distal radius fractures are the most common fractures of the upper extremity, representing approximately 75% of fractures in the forearm (1). While fractures occur in young patients as a result of high energy trauma, in the elderly they usually occur as a result of low-energy trauma such as a fall from standing height (2). The type of fracture depends on the position of the hand at the time of trauma and the amount of energy exposed. The type of fracture also varies depending on the quality of the bone (3).

In distal radius fractures, posteroanterior and lateral radiographs are often sufficient for diagnosis and the treatment. In the AP radiographs, the inclination of the radial joint surface, the condition of the radial process and ulnar styloid process, displacement and comminution of the distal fragment, cast indices, and the position of the wrist are evaluated. In lateral radiography, the angulation of the distal fragment relative to the dorsal or palmar surfaces and the angle of the distal articular surface of the radius and cast indices are evaluated. Oblique views are ordered when deemed necessary to evaluate the relationship of the fracture to the joint, to detect carpal bone fractures and carpal bone instability (4). Radiological parameters that guide the treatment and frequently used in radiological follow-up are radial inclination, radial height, articular step-off, second metacarpal-radius angle, stewart index, three-point index (TPI), cast index and padding (PAD) index (5-11).

When choosing the type of treatment, factors such as fracture type, patient's age, lifestyle, comorbidities, treatment compliance, and physical and mental capacity should be evaluated together (12,13). Closed reduction and casting are the preferred treatment methods in 84% of the cases which are considered as conservative treatments (14).

The aims of this study were to determine which radiological parameter/parameters had the higher predictive value to determine loss of reduction during conservative treatment and to present the functional status of individuals with and without loss of reduction at 6th month of the treatment. Thus, we hypothesized that the radiological parameters such as radial inclination, radial height, articular step-off, TPI, cast index, and PAD index had predictive value in the maintenance of reduction during conservative treatment of distal radius fractures.

Methods

Study Design and Ethical Issues

In this retrospective study, clinical and radiological data of the patients who were diagnosed as having distal radius fractures and received conservative treatment in our clinic between February 2019 and July 2020 were evaluated. Ethical approval for this study was obtained from University of Health Sciences Türkiye, Ankara City Hospital, Clinical Research Ethics Committee (decision no: E1/1133/2020, date: 30.09.2020). Written and verbal consents were obtained from the patients.

Participants and Follow-up

To evaluate whether the sample size used in this study was sufficient, a post-hoc power analysis was performed using G*Power 3.1. With an effect size of 0.30, an alpha level of 0.05, and a total sample size of 146, the achieved statistical power (1-β) was calculated as 0.81, indicating that the study had adequate power to detect the expected effect. The inclusion criteria for the study were; a) being between the ages of 18 to 65 years old, b) having a distal radius fracture treated conservatively, c) willing to participate in the study, d) having regular check-ups during the treatment, and e) having a clinical evaluation at the 6th month. The exclusion criteria from the study were; a) being incompatible with treatment and follow-up, b) having planned surgical treatment after admission, c) having an open distal radius fracture, and d) having a history of previous wrist fracture.

Assessment

A total of 146 patients who met the inclusion criteria were evaluated. Fractures were reduced with an appropriate reduction maneuver and all patients were applied a short or long arm cast, depending on the decision of the team working that day.

As stated in the literature, the following criteria were used to determine the adequacy of the reduction: 1. Shortening less than 5 mm in distal radioulnar joint compared to the healthy side, 2. On AP radiographs 21-28° radial inclination, 3. On lateral radiographs volar tilt between 0-20°, 4.

Articular step-off less than 2 mm (15). Patients were called the next day to check their swelling and their cast was bivalved if indicated. When the swelling subsided, the splint was replaced with a cast, and the post-reduction radiographs taken at that time were included in the study.

A new reduction maneuver was performed, and a new circular cast was applied to patients whose reduction loss was detected in early control radiographs. In these patients, the day their second cast was applied was considered the day the treatment started. All patients were called for follow-ups at 1st, 3rd and 5th weeks. In patients who had a long-arm circular cast, the cast was changed to a short-arm cast in the third week. The casts were removed at 5th week and patients in whom healing was suspected to be inadequate were applied a static wrist brace for one week.

a) Radiological Assessment

The radiographs were evaluated and the fractures were classified according to Frykman and Arbeitsgemeinschaft für Osteosynthesefragen (AO)/Orthopaedic Trauma Association (OTA) classification (16). In the Frykman classification, fractures are classified into 8 different types, ranging from Type 1 to Type 8, based on their relationship to the ulna styloid, radiocarpal joint and radio ulnar joint. In Type 3, Type 4, Type 7 or Type 8, the fracture extends to the radiocarpal joint (17). The AO/OTA classification is the most frequently used classification system today and is considered prognostically guiding. According to this classification, fractures are classified as B1, B2, B3, C1, C2 or C3 according to the extend to the distal radius joint. Radiological calculations were made by the researchers whose expertise field was orthopaedics.

Radial Inclination: On AP radiographs, the angle between the line drawn from the tip of the radial styloid to the radioulnar corner and the horizontal lines perpendicular to the long axis of the radius (5,6).

Radial Height: It is defined as the distance between the horizontal line perpendicular to the long axis of the radius from the radial styloid on the AP radiographs and the parallel lines tangent to the distal joint surface of the ulna (5,6).

Articular Step-off: It is a measurement that expresses the space between joint fragments. On direct x-rays, a gap of 2 mm or less is recommended (6).

Three-point Index (TPI): In conservatively treated distal radius fractures, the TPI, developed by Alemdaroğlu et al. (9), has been demonstrated to be the most statistically significant predictor of re-displacement of surgical variables. It embodies the fundamentals of fracture treatment, such as three-point fixation and appropriate anatomical reduction (18). A TPI of 0.8 or higher resulted with a relative risk of 46 for fracture re-displacement, according to data from Alemdaroğlu et al. (9) The radial TPI was computed as (a+b+c)/d using the measurements of the plaster cast and soft tissue on the radial side at the level of the radius's distal epiphyseal line (a), the ulnar side space in the fracture line (b), the radial side space at the level of the radial tubercle's beginning (c), and the total external diameter of the proximal radius at the level of the fracture line (d) on the anteroposterior (AP) radiograph (19). Three values were added together and written into the numerator. Following this measurement, the contact fracture surface at the distal radius was calculated and written in the denominator. Then, in the lateral radiograph, in accordance with the rules observed in the AP radiograph, the dorsal cast spaces and the volar cast space at the level of the fracture line were measured and written in the numerator. Thus, the mathematical value of the TPI defined for radius distal end fractures was obtained by adding the ratios obtained from AP and lateral radiographs. Examples of radiographs are presented in Figure 1 and Figure 2.

Cast Index: It is defined as the ratio of AP and lateral diameter at the fracture level after reduction and casting in distal radius fractures. The normal value is accepted as <0.8 (10). Examples of radiographs are presented in Figure 3.

PAD Index: It is the ratio between the interosseous space closest to the fracture on the AP radiograph and the widest space closest to the fracture line on the lateral radiograph, and its normal value is stated as <0.3 (11).

b) Functional Assessments

At the 6th month of the treatment, QuickDASH was performed to assess upper extremity functions and symptoms, the Mayo wrist score to rate the functional status of the wrist, and the visual analog scale (VAS) to assess the pain (20-22).

Statistical Analysis

Statistical analyzes were performed using SPSS version 18 software. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Simirnov tests). Descriptive statistics were given as mean ± standard deviation for normally distributed variables, and using median and interquartile range for non-normally distributed variables (using frequency tables for ordinal variables). Chi-square test was used to compare the results of radiological evaluation after reduction between individuals with and without reduction loss. Independent sample t-test was used to compare VAS, QuickDASH and Mayo means in patients with and without reduction loss. Regression analysis was performed to evaluate the effect of plaster indices on loss of reduction in fractures extending and not extending to the distal radial joint surface. The significance level was accepted as <0.05.

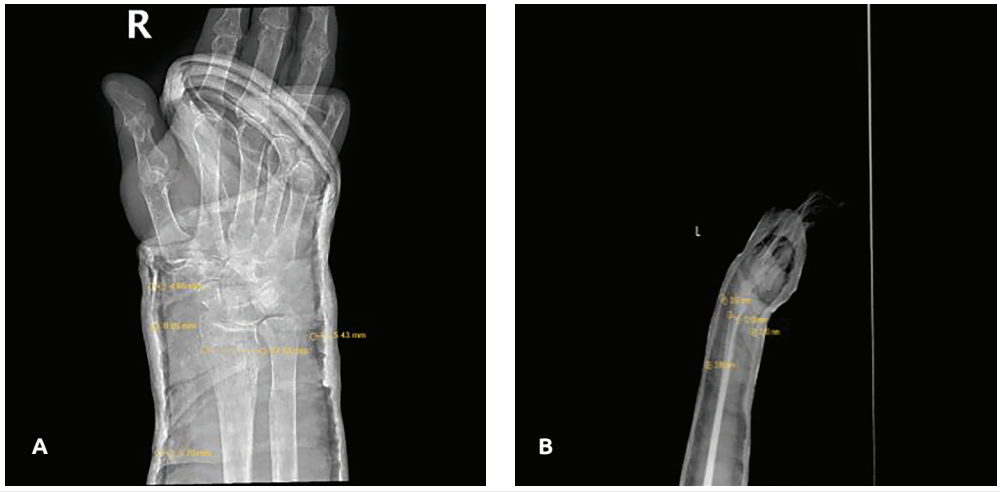

Figure 1. Patient with AO type B2, Frykman Type 3 fracture, whose treatment was completed without loss of reduction (A: Antero-posterior view, B: Lateral view) (TPI >0.8)

AO: Arbeitsgemeinschaft für Osteosynthesefragen, TPI: Three-point index

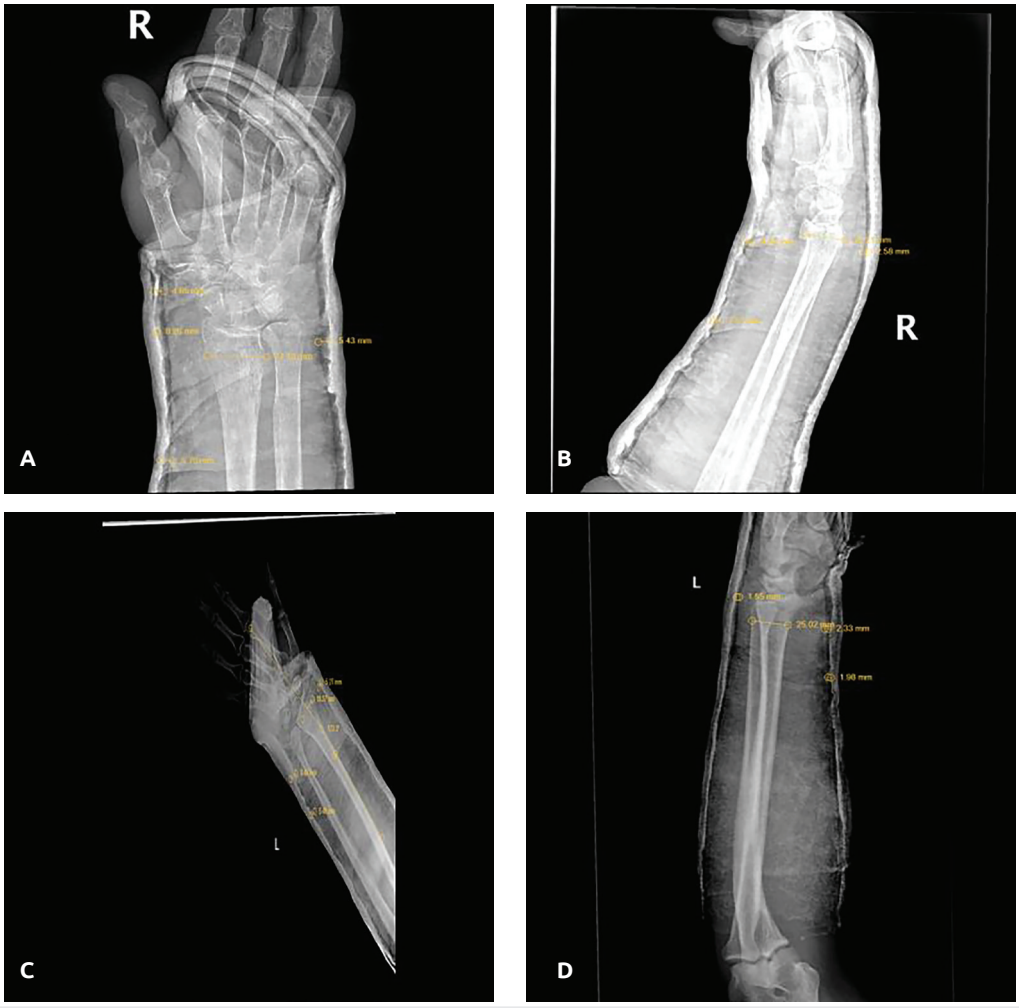

Figure 2. Patient with AO type B3, Frykman Type 3 fracture; TPI >0.8 before reduction (A,B); TPI <0.8 after reduction (C,D) (A: Antero-posterior view, B: Lateral view, C: Antero-posterior view, D: Lateral view)

AO: Arbeitsgemeinschaft für Osteosynthesefragen, TPI: Three-point index

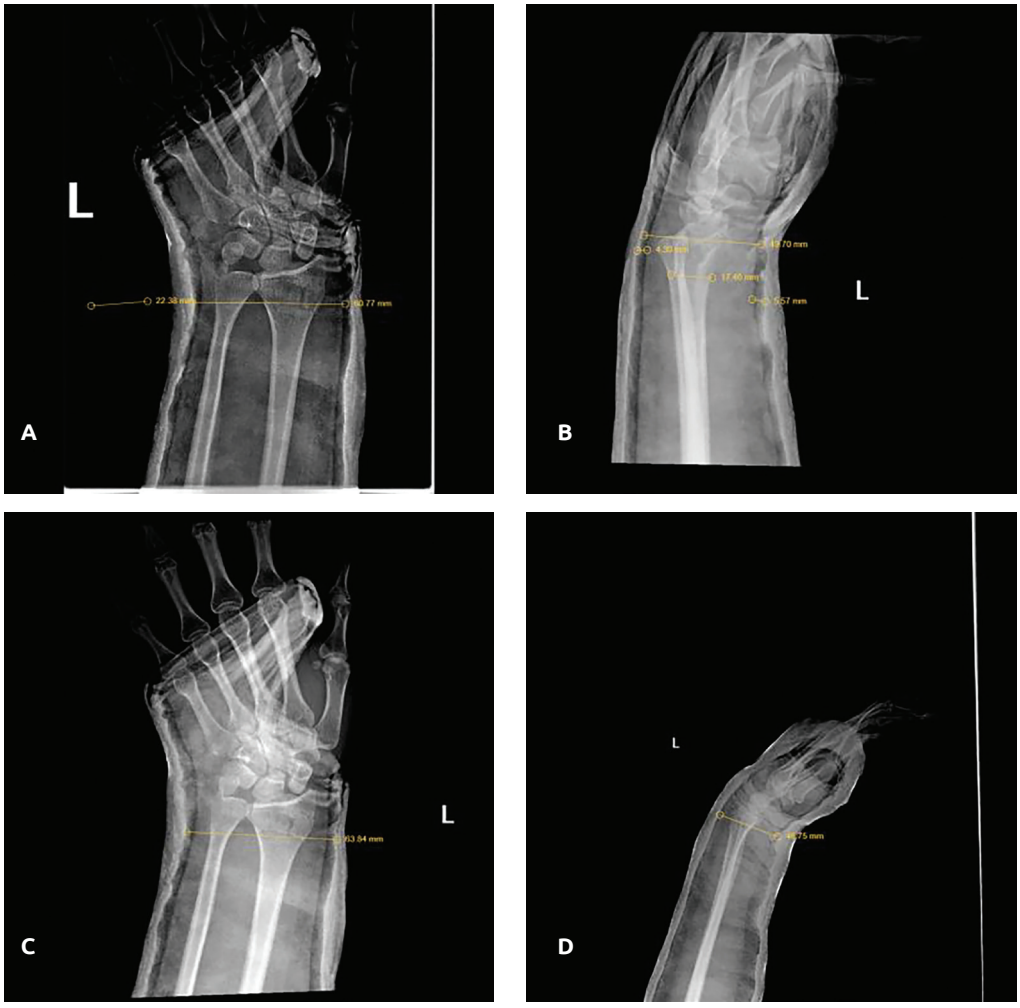

Figure 3. Patient with AO type A2, Frykman type 5 fracture; cast index >0.8 after first reduction (A,B); cast index <0.8 after rereduction (C,D) (A: Antero-posterior view, B: Lateral view, C: Antero-posterior view, D: Lateral view)

AO: Arbeitsgemeinschaft für Osteosynthesefragen

Results

Table 1 shows the patients' sociodemographic characteristics and characteristics related to the Frykman and AO classification. The mean age of the individuals included in the study (n=146) was 40.17±13.30 (min-max: 19-65) and 115 (78.8%) were male and 31 (21.2%) were female. According to the Frykman classification, 15 fractures (10.3%) were Type 1, 11 (7.5%) were Type 2, 25 (17.1%) were Type 3, 43 (29.5%) were Type 4, 11 (7.5%) were Type 5, 16 (11%) were Type 6, 15 (10.3%) were Type 7, 10 (6.8%) were Type 8; while according to AO classification, 31 (21.2%) were A2, 23 (15.8%) were A3, 8 (5.5%) were B1, 18 (12.3%) were B2, 18 (12.3%) were B3, 20 (13.7%) were C1, 20 (13.7%) were C2, 8 (5.5%) were C3.

A loss of reduction was observed in 31 (21.2%) of the individuals included in the study the comparison of post reduction radiological evaluation results between individuals with and without loss of reduction was shown in Table 2. A statistically significant difference was found between individuals with and without loss of reduction in terms of articular step-off, TPI, and cast indices ($p<0.05$). Considering the result of Bonferroni correction in the post-hoc analysis ($p<0.017$), the articular step-off difference between individuals with and without loss of reduction originated from the group with gap <2 mm.

The results of the logistic regression analysis performed to examine the effect of cast indices on loss of reduction in fractures with or without extension to the distal radius joint were given in Table 3 and Table 4. For the loss of reduction, the predictive value of TPI [95% confidence intervals (CI) (13.33, 1638.60)] was found the highest amongst the others in fractures extended to the distal radial articular surface (Table 3), according to both the AO and Frykman classifications while the predictive value of cast index [95% CIs (7.55, 1540.44)] was higher than the others in fractures that did not extend to the distal radial articular surface ($p<0.05$) (Table 4).

The findings regarding the functional scores showed that 76% (n=111) of the individuals had a QuickDASH score of "very good", 80.1% (n=117) had a Mayo score of "very good", and 80.8% (n=118) had a VAS score of 2 and below. The differences between the functional scores of the individuals with and without loss of reduction were given in Table 5. Accordingly, the VAS score at 6th month was significantly higher in individuals with loss of reduction ($p<0.05$).

Discussion

In this study, 21.20% of the patients experienced loss of reduction after the first intervention contrary to the literature which demonstrated higher patient ratio with loss of reduction as 78% in the study of Makhni et al. (23) and 69% in the study of Chang et al. (24). The low rate of patients with loss of reduction may be due to cases aged over 65 not being included in the study. Thus, it can be concluded that conservative treatment for fractures in middle adulthood, when bone quality and healing are better, has a higher success rate.

Table 1. Sociodemographic characteristics of the patients and their characteristics related to the Frykman and AO classification (n=146)

Age (mean ± SD)	**40.17±13.30**
	n (%)
Gender	
Male	115 (78.8)
Female	31 (21.2)
Frykman classification	
Type 1	15 (10.3)
Type 2	11 (7.5)
Type 3	25 (17.1)
Type 4	43 (29.5)
Type 5	11 (7.5)
Type 6	16 (11)
Type 7	15 (10.3)
Type 8	10 (6.8)
AO classification	
A2	31 (21.2)
A3	23 (15.8)
B1	8 (5.5)
B2	18 (12.3)
B3	18 (12.3)
C1	20 (13.7)
C2	20 (13.7)
C3	8 (5.5)

AO: Arbeitsgemeinschaft für Osteosynthesefragen, SD: Standard deviation

An articular step-off of 2 mm or more is defined as the space between the joint fragments in the distal radius joint. This is an indication for surgical intervention and changes in the articular step-off are considered an important parameter that indicating loss of reduction and necessitating re-reduction (25). In current study, 70.5% of the individuals had a articular step-off ≤2 mm and most of the remaining individuals had >2-<3 mm articular step-off. Considering that articular step-off was one of the indicators for surgical intervention, our findings were consistent with those in the literature and confirmed that the patients were suitable for conservative treatment. However the results of studies examining the effect of articular step-off on loss of reduction and functional scores vary. One study reported articular step-off was reported as an important determinant of loss of reduction and one of the basic criteria for reduction follow-up (24). However others such as Jaremko et al. (25) and Synn et al. (26) have stated that articular step-off is effective in re-reduction but does not

Table 2. Comparison of post reduction radiological evaluation results between individuals with and without reduction loss

	Loss of reduction		χ^2	**p**
	Present (n=31) n (%)	**Absent (n=115) n (%)**		
Radial inclination				
≤25	19 (61.3)	71 (61.7)	0.02	0.96
>25	12 (38.7)	44 (38.3)		
Articular step-off				
<2 mm	17 (54.80)	86 (74.80)	7.69	**0.02**
2-3 mm	10 (32.30)	26 (22.60)		
>3 mm	4 (12.90)	3 (2.60)		
Radial height loss				
<2 mm	15 (48.4)	64 (55.7)	2.24	0.68
2-4 mm	15 (48.4)	41 (35.7)		
>4 mm	1 (3.2)	10 (8.7)		
Three-point index				
≤0.8	13 (15.3)	72 (84.7)	4.29	**0.03**
>0.8	18 (29.5)	43 (70.5)		
Cast index				
≤0.8	15 (23.8)	48 (76.2)	4.44	**0.05**
>0.8	16 (19.3)	67 (80.7)		
PAD index				
≤0.3	19 (28.8)	47 (71.2)	4.11	0.06
>0.3	12 (15.0)	68 (85.0)		

χ^2: Chi-square test, PAD: Padding

Table 3. The effect of cast indexes on loss of reduction in fractures extending to the distal radial articular surface (n=146)

		Multivariable analysis		
	B	**OR**	**95% CI**	**p**
AO classification (B1, B2, B3, C1, C2, C3)				
TPI	4.99	147.820	13.33-1638.60	**0.000**
Cast index	-4.42	0.010	0.01-0.15	**0.001**
PAD index	0.21	1.230	0.12-11.91	0.853
Frykman classification (Type 3, Type 4, Type 7, Type 8)				
TPI	5.25	191.730	17.23-2132.40	**0.000**
Cast index	-4.68	0.090	0.00-0.13	**0.001**
PAD index	0.39	1.49	0.14-14.84	0.73

AO: Arbeitsgemeinschaft für Osteosynthesefragen, TPI: Three-point index, PAD: Padding, CI: Confidence interval, OR: Odds ratio

Table 4. The effect of cast indexes on loss of reduction in fractures that do not extend to the distal radial articular surface (n=146)

		Multivariable analysis		
	B	**OR**	**95% Cl**	**p**
AO classification (A2, A3)				
TPI	-5.25	0.005	0.00-0.05	**0.000**
Cast index	4.68	107.863	7.55-1540.44	**0.001**
PAD index	-0.39	0.671	0.67-6.69	0.734
Frykman classification (Type 1, Type 2, Type 5, Type 6)				
TPI	-5.25	0.005	0.00-0.05	**0.000**
Cast index	4.68	107.863	7.55-1540.44	**0.001**
PAD index	-0.39	0.671	0.67-6.69	0.734

AO: Arbeitsgemeinschaft für Osteosynthesefragen, TPI:Three-point index, PAD: Padding, CI: Confidence interval, OR: Odds ratio

Table 5. Comparison of functional scores in individuals with and without loss of reduction

Loss of reduction				
	Present (n=31) x̄ ± SD	**Absent (n=115) x̄ ± SD**	**Test***	**p**
VAS	2.41±1.02	1.79±1.07	0.015	**0.04**
QuickDASH	11.27±3.66	10.28±3.90	0.550	0.19
Mayo wrist score	90.16±5.55	92.21±6.42	2.310	0.08

VAS: Visual analog scale, *: Independent sample t-test

affect functional scores. In this study, loss of reduction was examined in different articular step-off classifications, and it was determined that there was a significant difference between the groups in terms of reduction continuation in favor of the group with articular step-off ≤2 mm which supported the literature concluding that articular step-off was important in loss of reduction and follow-up.

It has been known that one of the most important undesirable consequences of conservative treatment is loss of reduction, and there are some radiological parameters and cast indices used to estimate it (27). However, it is still unclear in the literature which of these parameters is more effective in predicting loss of reduction (7,18). It was shown that there was no significant relationship between radial inclination angle and loss of reduction and functional scores in the literature (28-30). Similarly, our results suggested that the radial inclination angle had no effect on predicting loss of reduction. In normal AP radiographs, the distance between the top of the radial styloid and the top of the distal radioulnar joint is defined as the radial height. According to some surgeons, changes in radial height value are indicators of surgery (31). For some surgeons, in conservative treatment, radial height is accepted as an important parameter for the loss of reduction and its follow-up (32). The results of studies examining the relationship between radial height, reduction loss and functional scores vary in the literature. In the study conducted by Maluta et al. (29), it was stated that radial height loss was not effective on loss of reduction andfollow-up, similar to the findings of Einsiedel et al. (33) and Földhazy et al. (34). On the other hand, it was found that radial height loss was effective on reduction follow-up and functional scores in a study (30). In another study, it was observed that radial height loss had an effect on functional scores (35). In current study, reduction loss was examined in different radial height losses, and it was determined that there was no difference in reduction loss between the groups. In this case, literature stating that radial height loss was not a criterion in reduction follow-up were also supported by our study.

Radiological indices used to monitor loss of reduction in conservative treatment of distal radius fractures with and without extension into the joint are TPI, cast and PAD indices. In literature, a few studies examined the relationship of TPI with loss of reduction as well as its effect according to the joint extension of the fracture. In a study conducted with adult patients, it was stated that TPI was not an important criterion in loss of reduction and follow-up (18), whereas in a study conducted on patients in the pediatric age group, TPI was found to be an important criterion in loss of reduction and follow-up (36). In another study conducted on patients in the pediatric age group, it was reported that TPI was not an important criterion in loss of reduction and follow-up (37). In current study, it was determined that TPI and cast indices were effective factors in predicting loss of reduction in fractures extending to the

distal radius joint according to the AO and Frykman fracture classification. It was determined that the most important factor predicting loss of reduction in fractures extending to the distal radius joint in the AO and Frykman fracture classifications was TPI. Accordingly, it can be said that TPI is the most effective index in monitoring loss of reduction in fractures extending into the joint.

Cast index is calculated as the ratio of the plaster gaps at the fracture level in AP and lateral radiographs and is expected to have a value of 0.8 or below (10). Although opinions regarding the effect of cast index on loss of reduction vary in the literature, few studies have been found regarding its effectiveness on fracture type in adult distal radius fractures. In the studies conducted on patients in the pediatric age group, it was stated that the cast index was important in monitoring loss of reduction and its follow-up (7,38). Similarly, it was reported that TPI was the most effective index in loss of reduction and follow-up in extra-articular fractures in adults (32). In this study, when the effects of TPI, cast and PAD indices were examined in fractures that did not extend to the distal radius joint according to the AO and Frykman Fracture classification; it was determined that TPI and cast indices had higher value in predicting loss of reduction. It was also determined that the most effective factor predicting loss of reduction in fractures that did not extend to the distal radius joint in the AO and Frykman fracture classifications was the cast index. Accordingly, it can be stated that cast index is the most effective index in the prediction of loss of reduction and its follow-up in fractures that do not extend into the joint.

Although the PAD index was reported as a protective factor against loss of reduction in a study conducted with pediatric patients by Ravier et al. (37). McQuinn and Jaarsma (39) stated the PAD index to be insignificant in reduction loss and follow-up. Similarly, Alemdaroğlu et al. (32) concluded that the PAD index had no effect on loss of reduction in their study with adult patients. In this study, it was determined that the PAD index was not an important factor in predicting loss of reduction in distal radius fractures; therefore, it was concluded that it was not necessary to use the PAD index in predicting and monitoring loss of reduction after distal radius fractures in adult patients.

Another parameter examined in our study was the change in functional scores of patients with and without loss of reduction. Regarding the effects of surgical and conservative treatment on long-term functional scores, it was stated that there was no difference between the two treatments, but the pain level was higher in patients who underwent surgical intervention (7). In the study, it was determined that there was no difference in functional scores between patients who underwent re-reduction and those who did not (24). Similarly in another study, it was shown that there was no difference in functional scores between patients who underwent reduction and those who did not (40). In this study, when functional scores were compared between patients with and without loss of reduction, it was observed that only the pain level of patients with loss of reduction was higher than those without loss of reduction. However, both groups recovered similarly in terms of functionality measured by QuickDASH and Mayo. Accordingly, considering the complications of surgical intervention, it may be recommended to re-reduce patients who develop loss of reduction and continue the treatment conservatively, assuming that it will not lead to functional loss.

Study Limitations

The retrospective study design and the lack of randomization and control group can be considered as the limitations of current study.

Conclusion

As a result of our study, it was seen that intra-articular stepping more than 2 mm was one of the most important parameters in loss of reduction. For reduction continuity, it was determined that the cast indices used had different effects depending on the fracture type. In our study, it was shown that TPI was the most effective parameter in predicting loss of reduction in fractures extending into the joint, and cast index was the most effective parameter in predicting loss of reduction in fractures that did not extend into the joint. In terms of functionality, it was determined that, after loss of reduction, re-reduction could lead to similar results to the recovery without loss of reduction.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from University of Health Sciences Türkiye, Ankara City Hospital, Clinical Research Ethics Committee (decision no: E1/1133/2020, date: 30.09.2020).

Informed Consent: Written and verbal consents were obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.C., A.U., B.Ö., Design: H.C., A.U., Data Collection or Processing: H.C., A.U., Analysis or Interpretation: H.C., Literature Search: H.C., Writing: H.C., A.U., B.Ö.

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Original Article

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Who is More Aggressive in the Race to Diagnose Pulmonary Embolism? General Practitioners or Emergency Medicine Specialists: A Multicenter Study

Pulmoner Emboli Tanısı Koyma Yarışında Kim Daha Agresif? Pratisyen Doktorlar mı Acil Tıp Uzmanları mı: Çok Merkezli Çalışma

Efe KANTER[1], Ejder Saylav BORA[1], Cüneyt ARIKAN[2], Fatma Nur KARAARSLAN[3], Merve ÖZTÜRK[1], Mesut AKYOL[1]

[1]İzmir Katip Çelebi University Faculty of Medicine, Department of Emergency Medicine, İzmir, Türkiye
[2]Dokuz Eylül University Faculty of Medicine, Department of Emergency Medicine, İzmir, Türkiye
[3]Manisa Soma State Hospital, Clinic of Emergency Medicine, Manisa, Türkiye

ABSTRACT

Objective: This study compared the rates of computed tomography pulmonary angiography (CTPA) requests, diagnostic yield and clinical outcomes between general practitioners and emergency medicine specialists with residents in suspected pulmonary embolism (PE).

Methods: This retrospective, multicenter, observational study was conducted in a tertiary education and research hospital and a secondary state hospital in Türkiye. Patients over 18 years of age who underwent CTPA for suspected PE were included. Demographic data, physician designation, CTPA results and emergency department outcomes were recorded. Diagnostic yield, admission and mortality rates were compared between groups.

Results: A total of 363 patients were included; the median age was 61 years (interquartile range: 48-72) and 52.3% were female. General practitioners evaluated 101 patients (27.8%), while specialists/residents evaluated 262 (72.2%). The overall PE positivity rate was 30.3%. Diagnostic yield was significantly higher in the specialist/resident group (37.4% vs. 11.9%, p<0.001). In multivariate analysis, evaluation by specialists/residents was identified as an independent predictor of PE diagnosis (odds ratio: 4.76, 95% confidence interval: 2.44-9.09,

ÖZ

Amaç: Bu çalışmada pratisyen hekimler ile acil tıp uzmanları ve asistanlarının pulmoner emboli (PE) ön tanısı ile istedikleri bilgisayarlı tomografi pulmoner anjiyografi (CTPA) oranları, tanısal verimlilikleri ve klinik sonuçları karşılaştırıldı.

Yöntemler: Retrospektif, çok merkezli bu gözlemsel çalışmaya Türkiye'de bir üçüncü basamak eğitim ve araştırma hastanesi ile bir ikinci basamak devlet hastanesi dahil edildi. Çalışmaya 18 yaş üstü, PE şüphesi ile CTPA çekilen hastalar alındı. Demografik veriler, hekim unvanı, CTPA sonuçları ve acil servis sonlanımları kaydedildi. Gruplar arasında tanısal verimlilik, yatış ve mortalite oranları karşılaştırıldı.

Bulgular: Çalışmaya toplam 363 hasta alındı; median yaş 61 (çeyrekler arası aralık: 48-72) idi ve %52,3'ü kadındı. Pratisyen hekimler 101 (%27,8), uzman/asistanlar 262 (%72,2) hastayı değerlendirdi. Genel PE pozitiflik oranı %30,3 idi. Tanısal verimlilik uzman/asistan grubunda belirgin şekilde yüksekti (%37,4 vs. %11,9, p<0,001). Multivaryant analizde uzman/asistan değerlendirmesi, PE tanısının bağımsız prediktörüydü (olasılık oranı: 4,76, %95 güven aralığı: 2,44-9,09, p<0,001). PE pozitif hastalarda taburculuk oranı daha düşük (%21,8 vs. %59,7), servis (%42,7 vs. %20,9) ve yoğun bakım yatış oranları

Address for Correspondence: Assoc. Prof. Cüneyt Arıkan, Dokuz Eylül University Faculty of Medicine, Department of Emergency Medicine, İzmir, Türkiye
E-mail: cuneyt.arikan@deu.edu.tr
ORCID IDs of the authors: E.K.: 0000-0002-0208-950X, E.S.B.: 0000-0002-2448-2337, C.A.: 0000-0001-6823-5357, F.N.K.: 0000-0003-4465-9598, M.Ö.: 0009-0006-3151-8250, M.A.: 0009-0005-3319-0482

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ABSTRACT

p<0.001). Among PE-positive patients, discharge rate was lower (21.8% vs. 59.7%), while ward admission rate (42.7% vs. 20.9%), intensive care unit admission rate (35.5% vs. 19.4%) and mortality (19.1% vs. 7.1%) were significantly higher.

Conclusion: Emergency medicine specialists and residents demonstrated greater diagnostic selectivity and markedly higher diagnostic accuracy compared with general practitioners. These findings emphasize the critical role of specialist involvement in PE diagnosis and suggest that structured decision support systems may enhance diagnostic efficiency among general practitioners in emergency settings.

Keywords: Diagnostic yield, emergency medicine, pulmonary embolism, tomography

ÖZ

(%35,5 vs. %19,4) ile mortalite (%19,1 vs. %7,1) anlamlı olarak daha yüksekti.

Sonuç: Acil tıp uzmanları ve asistanlarının CTPA isteminde daha seçici davrandığı ve tanısal doğruluklarının pratisyen hekimlere göre belirgin şekilde yüksek olduğu gösterilmiştir. Bulgular, uzman katkısının acil servislerde PE tanısında kritik rol oynadığını ve yapılandırılmış klinik karar destek sistemlerinin pratisyen hekimler için tanısal verimliliği artırabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Tanısal verimlilik, acil tıp, pulmoner emboli, tomografi

Introduction

Pulmonary embolism (PE) is a serious clinical condition with high mortality that requires urgent intervention, most often resulting from acute obstruction of the pulmonary arteries by thromboembolism as a complication of deep vein thrombosis. PE presents to emergency departments with non-specific symptoms such as sudden dyspnea, chest pain, syncope, tachycardia or hypoxemia, which makes diagnosis challenging, although early recognition and prompt treatment are life-saving (1,2).

Accurate clinical assessment, the use of risk stratification tools such as the Wells score and timely referral for appropriate imaging play a critical role in the diagnostic process (3). Computed tomography pulmonary angiography (CTPA) is considered the gold standard imaging modality in the diagnosis of PE and is frequently employed in emergency department algorithms. However, unnecessary use of this examination may lead to avoidable radiation exposure for patients as well as inefficient utilization of healthcare resources (4-6). Therefore, the accuracy of physicians' decisions to request imaging in suspected PE and the impact of these decisions on diagnostic yield are of great importance (4,7).

In Türkiye, both general practitioners and emergency medicine specialists as well as residents are involved in patient care in emergency departments. Although this distribution of responsibilities varies among hospitals, differences in clinical approach between these physician groups may influence diagnostic decision-making. Physicians with specialty training are expected to perform more systematic evaluations and to base their clinical reasoning on evidence-based guidelines, which may in turn affect diagnostic accuracy (8,9).

In this study, we investigated the extent to which general practitioners and emergency medicine specialists with residents requested imaging for suspected PE, the diagnostic yield and accuracy of these examinations and evaluated the role of physician designation in the diagnostic process within a multicenter study design. Although many studies have evaluated diagnostic yield and utilization of CTPA in suspected PE, to our knowledge, no study has directly compared the diagnostic efficiency of general practitioners versus emergency medicine specialists in emergency settings. This gap is critical, since physician expertise may significantly affect diagnostic accuracy, radiation exposure, and resource utilization. Our study aimed to fill this gap through a multicenter design.

Methods

Study design and Setting

This study was a retrospective, multicenter, observational analysis conducted in two hospitals in Türkiye. The study included two centers, one being a tertiary education and research hospital and the other a secondary state hospital. Data were collected between January 1, 2022 and June 30, 2023, covering an 18-month period. The study was initiated after obtaining approval from the Local Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 0432, date: 21.09.2023) and administrative authorization from the other participating center.

Study Population

Inclusion Criteria

1. Patients aged over 18 years

2. Patients presenting with clinical suspicion of PE for whom CTPA was requested with this preliminary diagnosis.

Exclusion Criteria

1. Patients younger than 18 years

2. Trauma patients

3. Patients with incomplete data

4. Patients whose outcomes could not be followed (those referred to another facility or those who refused treatment).

Study Protocol and Data Collection

In both centers, a similar protocol was followed. Patients presenting to the emergency department were referred for CTPA with a preliminary diagnosis of PE based on clinical suspicion and physician assessment. The decision-making process considered presenting symptoms (dyspnea, chest pain, syncope, tachycardia, hypoxemia, etc.), vital signs, laboratory findings and accompanying clinical risk factors. No standardized clinical decision algorithm was mandated and each center adhered to its routine clinical practice.

Although validated clinical prediction tools such as the Wells, Geneva or YEARS scores were available in both centers, they were not systematically integrated into daily practice. Therefore, CTPA requests were primarily based on clinical judgment and physician discretion.

Data collection was performed through the hospital information management systems of both centers. Records were retrospectively reviewed, all patients who underwent CTPA during the study period were identified and personal identifiers were anonymized. For each patient, age, sex, presenting complaint, physician designation (general practitioner or emergency medicine specialist), CTPA result, additional clinical diagnoses and emergency department outcome were recorded. CTPA results were classified as PE positive or negative based on radiology reports.

From these data, the total number of emergency visits, the rate of CTPA requests, the proportion of positive PE diagnoses and their distribution according to physician groups were calculated. In addition, hospitalization and mortality outcomes for patients diagnosed with PE were documented. To ensure accuracy, all records were reviewed by independent researchers in both centers and verified prior to analysis.

Outcomes

Primary Outcome

The primary objective of this study was to compare the frequency of requesting diagnostic tests for PE between specialists and general practitioners relative to the overall emergency department population and to determine the incidence of confirmed PE within this patient cohort.

Secondary Outcome

The secondary objective was to investigate whether there were differences between specialists and general practitioners in patients diagnosed as having PE.

Statistical Analysis

All statistical analyses were performed using IBM SPSS version 27. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Variables that did not show normal distribution were expressed as median with interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages. Comparisons of continuous variables between groups were conducted using the Mann-Whitney U test. Categorical variables were compared using the chi-square test.

To evaluate the diagnostic yield of CTPA requests, the proportion of positive PE diagnoses was calculated for each physician group and compared using the chi-square test. Clinical outcomes [discharge, ward admission, intensive care unit (ICU) admission] and mortality rates were also compared between groups, as well as between patients with and without PE.

Univariate logistic regression analyses were initially performed to identify potential predictors of PE diagnosis. Multivariate logistic regression was performed to identify independent predictors. Odds ratios (OR) with 95% confidence intervals (CI) were reported. A p value <0.05 was considered statistically significant.

Results

A total of 363 patients who underwent CTPA during the study period were included in the analysis. The median age was 61 years (IQR: 48-72) and 52.3% were female. Specialists/residents evaluated 262 patients (72.2%), while general practitioners evaluated 101 patients (27.8%). PE was confirmed in 110 patients (30.3%). Regarding clinical outcomes, 48.2% of patients were discharged from the emergency department, 27.5% were admitted to wards and 24.2% required ICU admission. The overall mortality rate was 10.7% (Table 1).

When stratified by physician group, the proportion of CTPA requests among all emergency department visits was higher in the specialist group compared to general practitioners

Table 1. Demographic and clinical characteristics and outcomes of study population

Characteristic		Median (IQR) or n (%)
Age		61 (48-72)
Gender	Female	190 (52.3)
	Male	173 (47.7)
Physician group	Specialists/residents	262 (72.2)
	General practitioners	101 (27.8)
Pulmonary embolism	None	253 (69.7)
	Present	110 (30.3)
Outcome	Discharged	175 (48.2)
	Ward admission	100 (27.5)
	ICU admission	88 (24.2)
Mortality	None	324 (89.3)
	Present	39 (10.7)

IQR: Interquartile range, ICU: Intensive care unit

(0.87% vs. 0.50%, p<0.001). The median age was slightly lower in the specialist group (60 vs. 65 years, p=0.037), while gender distribution was similar between the groups (p=0.208). The diagnostic yield (efficiency index) of CTPA was significantly higher in the specialist group compared to general practitioners (37.4% vs. 11.9%, p<0.001) as shown in Figure 1 and Table 2. Differences in clinical outcomes were also observed, with general practitioners' patients more frequently admitted to wards, while specialists' patients were more often discharged or admitted to the ICU (p<0.001). Mortality rates did not differ significantly between the groups (p=0.316) (Table 2).

Table 3 shows the comparison of patients according to PE status demonstrated significant differences in clinical outcomes. Discharge was less common among PE-positive patients compared to those without PE (21.8% vs. 59.7%), whereas ward admissions (42.7% vs. 20.9%) and ICU admissions (35.5% vs. 19.4%) were more frequent in the PE-positive group (p<0.001). Mortality was also higher in the PE-positive group (19.1% vs. 7.1%, p=0.002).

According to Table 4, patients evaluated by specialists/residents had significantly higher odds of a positive PE diagnosis compared to those evaluated by general practitioners (OR: 4.76, 95% CI: 2.44-9.09, p<0.001). Neither age (p=0.065) nor gender (p=0.723) were independent predictors of PE diagnosis.

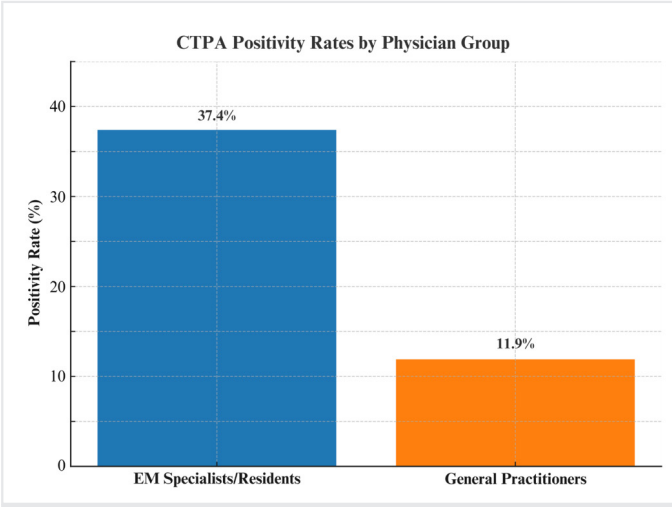

Figure 1. CTPA positivity rates by physician group

CTPA: Computed tomography pulmonary angiography, EM: Emergency medicine

Table 2. Comparison of characteristics and outcomes by physician group

Variable, n (%)		Specialists/residents (n=262)	General practitioners (n=101)	p†
CTPA requests / ED visits‡		262/30,000 (0.87%)	101/20,000 (0.50%)	**<0.001**
Age [Median (IQR)]		60 (47-70)	65 (50-74)	**0.037**
Gender	Female	143 (54.6)	47 (46.5)	0.208
	Male	119 (45.4)	54 (53.5)	
Pulmonary embolism	Present	98 (37.4)	12 (11.9)	**<0.001**
	None	164 (62.6)	89 (88.1)	
Outcome	Discharged	170 (64.9)	5 (5.0)	**<0.001**
	Ward admission	47 (17.9)	53 (52.5)	
	ICU admission	45 (17.2)	43 (42.6)	
Mortality	Present	25 (9.5)	14 (13.9)	0.316
	None	237 (90.5)	87 (86.1)	

‡: Approximate total ED visits during the study period, †: Mann-Whitney U test for continuous variables, chi-square test for categorical variables, CTPA: Computed tomography pulmonary angiography, ED: Emergency department, IQR: Interquartile range, ICU: Intensive care unit

Table 3. Clinical outcomes and mortality according to pulmonary embolism status

Variable, n (%)		PE present (n=110)	PE absent (n=253)	p†
Outcome	Discharged	24 (21.8)	151 (59.7)	**<0.001**
	Ward admission	47 (42.7)	53 (20.9)	
	ICU admission	39 (35.5)	49 (19.4)	
Mortality	Present	21 (19.1)	18 (7.1)	**0.002**
	None	89 (80.9)	235 (92.9)	

†: Chi-square test for categorical comparisons, PE: Pulmonary embolism, ICU: Intensive care unit

Table 4. Logistic regression analyses for predictors of pulmonary embolism

Variable	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p†
Physician group‡	4.33	(2.38-7.99)	<0.001	4.76	(2.44-9.09)	**<0.001**
Age	1.01	(0.99-1.02)	0.208	1.01	(1.00-1.03)	0.065
Gender (male)	0.98	(0.62-1.53)	0.923	1.09	(0.68-1.74)	0.723

‡: Reference category: general practitioners, †: Univariate and multivariate logistic regression analyses, OR: Odds ratio, CI: Confidence interval

Discussion

This study aimed to highlight the differences in diagnosing PE between secondary and tertiary emergency departments. In particular, the comparison of CTPA utilization rates, diagnostic yield and clinical outcomes between physician groups has been scarcely addressed in the literature. Although CTPA remains the gold standard imaging modality in the diagnosis of PE, it is a tool that must be carefully considered in clinical decision-making due to both its diagnostic value and the risk of overuse. In this respect, our study provides an original contribution by focusing on an important aspect of clinical practice.

In our cohort of 363 patients, PE was confirmed in 30.3%. This rate was higher than many previously reported studies. For instance, Yazgan et al. (10) reported a positivity rate of 20.8% in a Turkish cohort of 696 patients. In contrast, Ozakin et al. (11) reported a rate of only 6.4% in a single-center study. A prospective cohort from Montreal reported 15.9% (12), the Sheffield series found 15.9% (13) and a study from Bahrain reported 12.2% (14). The 30.3% rate in our study is above the upper values reported in international literature, suggesting that patient selection in our cohort may have been relatively more accurate.

The diagnostic yield of CTPA has been reported to vary widely in the literature. In a study including 974 patients, Walen et al. (15) reported a diagnostic yield of 23% (n=224), a value that lay at the higher end of previously reported ranges. In contrast, a multicenter study conducted in Western Australia examining trends between 2003 and 2015 demonstrated that the diagnostic yield declined to as low as 5.7%, raising concern regarding the potential overuse of CTPA (16). The 30.3% positivity rate in our study is considerably higher compared to these large series, reflecting a more selective approach in clinical decision-making.

Among patients diagnosed as having PE, the discharge rate was low (21.8%), while ward admission rate (42.7%) and ICU admission rate (35.5%) were significantly higher. In contrast, the discharge rate in PE-negative patients was 59.7% (p<0.001). Mortality was also higher in the PE-positive group (19.1% vs. 7.1%, p=0.002). These results underscore the significant clinical burden of PE in emergency care and its impact on patient prognosis. Similarly, studies from Canada reported high admission rates among PE-positive patients (17) and data from Sheffield supported this finding (13).

The most striking finding of our study was the marked difference between physician groups. The positivity rate of CTPA was 37.4% among specialists/residents, compared with only 11.9% among general practitioners (p<0.001). Moreover, multivariate logistic regression analysis revealed that patients evaluated by specialists/residents had nearly a 4.8-fold higher likelihood of receiving a PE diagnosis compared with those assessed by general practitioners (OR: 4.76, 95% CI: 2.44-9.09, p<0.001). These results indicate that emergency medicine specialists request CTPA more selectively and that their diagnostic efficiency stands out as an independent predictor of accurate diagnosis.

The overuse of CTPA and false positives remain an important debate in the literature. Hutchinson et al. (18) reported false positive rates as high as 59.4% at the subsegmental level. National Institute for Health and Care Excellence and the Royal College of Radiologists guidelines recommend an acceptable CTPA positivity rate between 15.4% and 37 (13,14). The 30.3% positivity rate in our study fell within this range, suggesting that overutilization was not evident. Thus, our findings supported the notion that CTPA was appropriately applied to a well-selected patient population.

In a retrospective study from Bahrain, the positivity rate was 12.2% (14), while studies from Canada reported 15% (17), Türkiye 20.8% (10) and the United Kingdom 15.9% (13). Conversely, the Western Australia study showed that CTPA use increased from 3.3 per 10,000 person-years in 2003 to 17.1 in 2015. Diagnostic yield initially increased from 12.7% in 2003 to 17.4% in 2005 but declined to 12.2% in 2015. These results indicate that despite increased use, diagnostic yield has trended downward over time (16). The 30.3% positivity rate in our study, when compared with both regional and international cohorts, stands out as remarkably high, supporting the possibility that greater involvement of specialists in tertiary centers contributes to higher diagnostic efficiency.

The 2019 European Society of Cardiology guidelines on acute PE emphasize the use of validated clinical prediction scores and D-dimer testing prior to CTPA to

optimize diagnostic efficiency (19). Our findings that specialists achieved higher positivity rates align with these recommendations, suggesting that adherence to structured diagnostic pathways is more consistently practiced by trained emergency physicians.

To our knowledge, there are almost no studies directly examining the diagnostic yield of CTPA requests according to physician groups. This aspect makes our study unique, demonstrating the diagnostic selectivity of specialists with objective data. General practitioners may have a tendency to screen a broader patient population, which could explain the lower positivity rates. These findings highlight the importance of structured training and decision support systems in emergency departments.

Accurate diagnosis of PE not only reduces unnecessary radiation exposure but also directly affects patient outcomes. The higher mortality rate observed among PE-positive patients in our cohort provides the most concrete evidence of this impact. Furthermore, the significantly increased ICU admission rate in the PE-positive group underscores the critical importance of early and accurate diagnosis in the management of these patients.

Study Limitations

This study has several important limitations. First, the individual components required to calculate clinical probability scores such as the Wells or revised Geneva scores were not fully accessible for every patient, which prevented the systematic calculation of these tools. Similarly, D-dimer levels and presenting clinical parameters were not consistently available for all cases. This limitation restricts the ability to evaluate the appropriateness of CTPA requests at the individual patient level.

Second, the anatomical distribution and thrombus burden of PE cases were not assessed. The clinical significance of findings limited to the subsegmental level is known to be variable, as these may be clinically relevant in some patients but of uncertain therapeutic necessity in others. The inability to make this distinction represents a limitation in the interpretation of our findings. Furthermore, markers of right ventricular strain or risk stratification tools such as the simplified PE severity index could not be systematically collected due to the retrospective design, limiting detailed assessment of PE severity and prognosis.

Third, the cross-sectional sample included only patients who underwent CTPA. This selection does not reflect the true prevalence of PE within the entire emergency department population nor does it provide a comprehensive assessment of the appropriateness of imaging indications. Instead, it represents physicians' thresholds and preferences for requesting imaging. Differences between secondary and tertiary centers such as patient demographics, triage procedures, time of presentation, bed and imaging availability, radiologist experience and institutional protocols were not measured and remained as potential confounders. In addition, as with any retrospective design, potential biases such as missing data, variability in documentation, and physician selection differences may have influenced the observed results.

These results highlight the potential role of structured decision-support systems and targeted training programs for general practitioners working in emergency departments. Future prospective studies should evaluate whether integrating such strategies can further improve diagnostic accuracy and patient safety.

Conclusion

This multicenter study showed that emergency medicine specialists and residents had a markedly higher diagnostic yield in detecting PE compared to general practitioners and physician expertise was identified as an independent predictor of accurate diagnosis. Furthermore, PE-positive patients demonstrated higher ward and ICU admission rates, highlighting the substantial clinical burden of this condition in emergency settings.

Our findings underscore the importance of specialist involvement in decision-making for suspected PE and suggest that broader use of standardized risk stratification tools and training for non-specialists may improve diagnostic accuracy and reduce unnecessary CTPA utilization.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Local Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 0432, date: 21.09.2023).

Informed Consent: Informed consent was not obtained due to the retrospective design of the study.

Footnotes

Authorship Contributions

Concept: E.K., E.S.B., C.A., Design: E.K., E.S.B., C.A., Data Collection or Processing: C.A., F.N.K., M.Ö., M.A., Analysis or Interpretation: E.K., F.N.K., M.Ö., M.A., Literature Search: E.K., E.S.B., C.A., F.N.K., M.Ö., M.A., Writing: E.K., C.A.

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Original Article

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Impact of Online Education on LAST Knowledge in Anesthesiology and Intensive Care Specialists

Anesteziyoloji ve Yoğun Bakım Uzmanlarında LAST Bilgisi Üzerine Çevrim İçi Eğitimin Etkisi

Ayşe Gül KOÇOĞLU KINAL[1], Yunus Emre AYHAN[2]

[1]University of Health Sciences Türkiye, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Intensive Care, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye

ABSTRACT

Objective: Local anesthetic systemic toxicity (LAST) is a rare but potentially life-threatening complication of local anesthetic use. Despite its clinical importance, medical specialists often have limited knowledge on this topic, and structured training is rarely implemented. This study aimed to evaluate the effectiveness of a brief, structured online educational module in improving knowledge of LAST among anesthesiology and intensive care specialists.

Methods: This cross-sectional pre-post study included anesthesiology and intensive care specialists in İstanbul. Participants completed a 15-item multiple-choice knowledge test before and after a short educational intervention. The educational content, adapted from UpToDate®, was presented as a two-page plain-text document designed for 3-4 minutes of reading. Wilcoxon signed-rank tests were used to compare pre- and post-intervention scores, and multiple linear regression was performed to identify predictors of baseline knowledge.

Results: A total of 200 participants completed both assessments. The mean knowledge score increased significantly from 11.7±1.7 to 12.8±1.2 after the intervention ($p<0.001$). Improvements were most notable in knowledge of risk factors, prevention, and lipid emulsion therapy. Regression analysis indicated that older age and prior LAST training were negatively associated with baseline knowledge, while anesthesiology specialization was a positive predictor.

ÖZ

Amaç: Lokal anestezik sistemik toksisitesi (LAST), lokal anestezik kullanımına bağlı nadir ancak potansiyel olarak ölümcül bir komplikasyondur. Klinik önemine rağmen tıp uzmanlarının bu konudaki bilgi düzeyinin sınırlı olduğu ve yapılandırılmış eğitimlerin yaygın olmadığı bilinmektedir. Bu çalışmada, anesteziyoloji ve yoğun bakım uzmanlarının LAST konusundaki bilgi düzeyini artırmak amacıyla hazırlanan kısa ve yapılandırılmış bir çevrim içi eğitim modülünün etkinliğinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel öncesi-sonrası tasarıma sahip anket çalışmasına, İstanbul'da görev yapan anesteziyoloji ve yoğun bakım uzmanları dahil edilmiştir. Katılımcılara, eğitim öncesi ve sonrası 15 soruluk çoktan seçmeli bilgi testi uygulanmıştır. Eğitim içeriği, UpToDate® kaynaklarından derlenmiş olup, sade metin formatında ve 3-4 dakikalık okuma süresiyle tasarlanmış iki sayfalık bir doküman olarak sunulmuştur. Eğitim öncesi ve sonrası bilgi puanları Wilcoxon işaretli sıralar testi ile karşılaştırılmış; başlangıç bilgi düzeyini etkileyen faktörler çoklu doğrusal regresyon analizi ile değerlendirilmiştir.

Bulgular: Toplam 200 katılımcı her iki değerlendirmeyi tamamlamıştır. Eğitim sonrası ortalama bilgi puanı anlamlı şekilde artmıştır (öncesi: 11,7±1,7; sonrası: 12,8±1,2; $p<0,001$). En fazla artış risk faktörleri, korunma stratejileri ve lipid emülsiyon tedavisine yönelik sorularda görülmüştür. Regresyon analizinde, ileri yaş ve daha önce LAST eğitimi almış olmak başlangıç bilgi düzeyiyle negatif ilişki gösterirken, anesteziyoloji uzmanlığı pozitif belirleyici olarak bulunmuştur.

Address for Correspondence: Yunus Emre Ayhan MD, University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye
E-mail: eczyunusemreayhan@gmail.com
ORCID IDs of the authors: A.G.K.K.: 0000-0002-6905-9532, Y.E.A.: 0000-0001-6093-0849

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ABSTRACT

Conclusion: A brief, focused online module significantly improved LAST-related knowledge among anesthesiology and intensive care specialists. These results emphasize the value of targeted education in enhancing preparedness for rare but critical complications in clinical practice.

Keywords: Local anesthetic systemic toxicity, anesthesiology, intensive care, online education, knowledge level

ÖZ

Sonuç: Kısa ve hedefe yönelik çevrim içi eğitim modülü, anesteziyoloji ve yoğun bakım uzmanlarının LAST konusundaki bilgi düzeyini anlamlı şekilde artırmıştır. Bu sonuçlar, nadir ancak kritik toksik komplikasyonlara hazırlık açısından yapılandırılmış eğitimlerin önemini ortaya koymaktadır.

Anahtar Kelimeler: Lokal anestezik sistemik toksisite, anesteziyoloji, yoğun bakım, çevrim içi eğitim, bilgi düzeyi

Introduction

Local anesthetics (LAs) are widely used by anesthesiologists, surgeons, emergency physicians, dentists, and other medical specialists in routine clinical practice (1). Despite their frequent use, awareness of LA systemic toxicity (LAST)—a rare but potentially life-threatening complication—remains limited (2-4). LAST can involve both the central nervous and cardiovascular systems and may occur with any type or route of LA administration (5,6).

Although the general safety of LAs is well-established, systemic toxicity remains a risk, especially with high doses, intravascular injection, or patient-specific factors (7). Preventive strategies such as ultrasound-guided administration have reduced the incidence of LAST, while therapeutic advances like lipid emulsion (LE) therapy have improved outcomes after toxicity occurs (4,7,8). Early recognition is essential, but previous studies have highlighted inadequate provider awareness, pointing to a need for improved education on prevention and management (2,4,9).

As clinicians directly responsible for administering LAs, anesthesiologists and intensive care specialists play a pivotal role in identifying and managing LAST. However, studies assessing their specific knowledge are scarce (4,10). In Türkiye, a prior study evaluated physicians' knowledge of LAST and LE therapy, mainly among LA users, highlighting important knowledge gaps (11). In one study, anesthesiology trainees demonstrated good understanding of symptoms, risk factors, LE therapy, and treatment protocols, though educational gaps still existed (4). In contrast, other research showed that physicians in non-anesthesiology specialties were often unaware of guideline-based treatment and LE use (2,12,13). These findings indicate a widespread necessity for structured education on LAST.

The primary aim of this study was to evaluate the effect of a brief, structured online educational module on the knowledge levels of anesthesiology and intensive care specialists regarding LAST. To our knowledge, this is among the few studies assessing such an intervention among experienced clinicians. The results are intended to support targeted educational strategies and contribute to safer clinical practices.

Methods

Study Design and Participants

This was a cross-sectional pre-post intervention study conducted via an online survey among anesthesiology and intensive care specialists working in İstanbul. The survey was distributed between February 14 and 22, 2025, via digital messaging platforms. The STROBE checklist was used to ensure reporting quality (14).

Ethics Approval and Consent to Participate

The study received ethical approval from the Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (decision no: 170, date: 06.02.2025) and written informed consent was obtained from all participants. All procedures adhered to the ethical standards and the principles of the 1964 Helsinki Declaration and its later amendments.

Study Procedure

The study was implemented using a single Google Forms link containing three sequential phases:

Pre-education Survey: A 15-item multiple-choice test evaluating participants' baseline knowledge of LAST.

Educational Material: A concise, two-page plain-text summary adapted from the UpToDate® resource titled Local Anesthetic Systemic Toxicity (accessed January 8, 2025). The educational material and the full knowledge questionnaire were provided as Supplementary Files 1 and 2, respectively. It covered key topics such as pathophysiology, clinical signs, risk factors, prevention, management, and LE therapy. Designed for 3-4 minutes of reading, the content directly aligned with the test items.

Post-education Survey: The same 15-item test was repeated to assess knowledge improvement.

Questionnaire Development

The questionnaire was based on an extensive literature review and UpToDate® content (1-3,6-8,15,16). A clinical pharmacist and an intensive care specialist reviewed items for relevance and clarity. English-Turkish back-translation ensured linguistic accuracy.

A pilot test-retest with 20 physicians not included in the main study was conducted to evaluate internal consistency and inter-rater agreement. The internal consistency of the questionnaire, assessed using Cronbach's alpha, was calculated as 0.67. Although this value is considered borderline, it may be explained by the multidimensional nature of the questionnaire, which encompasses diverse domains of LAST. Two independent raters scored the same set of responses, and the item-level agreement showed moderate concordance (Cohen's kappa=0.588). A detailed contingency table is provided in Supplementary File 3.

The survey had two sections:

Sociodemographic data (10 items)

Knowledge and self-evaluation on LAST management (5 items)

Knowledge test (15 items) divided into seven domains:

LAST mechanism (Q1,2)

Pathophysiology (Q3,4)

Epidemiology (Q5,6)

Risk factors and prevention (Q7,8)

Clinical features (Q9,10)

Management (Q11,12)

LE therapy (Q13-15)

Each correct answer was scored as 1 point; total scores ranged from 0 to 15. Scores were categorized as low (0-5), moderate (6-10), and high (11-15).

Inclusion and Exclusion Criteria

Inclusion criteria were active employment as an anesthesiology or intensive care specialist in İstanbul and voluntary participation. Incomplete or duplicate responses were excluded.

Sample Size

Based on the estimated number of anesthesiology and intensive care specialists in İstanbul (approximately 1,000), the required sample size for a 95% confidence level and a 6% margin of error was calculated as 260. Although only 200 participants completed both the pre- and post-intervention questionnaires, this sample size was considered sufficient for within-subject statistical comparisons. A post-hoc power analysis confirmed that the study retained high statistical power (1-β=0.999) for paired t-tests.

Statistical Analysis

Categorical variables were reported as frequencies and percentages; continuous variables were expressed as mean ± standard deviation or median [interquartile range (IQR)]. Continuous variables were evaluated for normality using the Kolmogorov-Smirnov test and visual methods (histograms and Q-Q plots). Mann-Whitney U and Kruskal-Wallis H tests were used to compare baseline knowledge scores across participant subgroups (e.g., specialty, gender, years of experience). The Wilcoxon signed-rank test was used to compare participants' self-assessed knowledge scores and objective knowledge test scores before and after the educational intervention. Post-hoc power analysis confirmed that the study had adequate power (1-β=0.999) for within-subject comparisons based on paired t-tests, despite the response rate not reaching the initially projected level. Cronbach's alpha and intraclass correlation coefficient tested internal consistency and reliability. Multiple linear regression identified predictors of baseline knowledge scores using age, gender, specialty, workplace, years of experience, and prior LAST training. A stepwise method was used. Regression results included coefficients, 95% confidence interval (CI), p-values, and R^2 values. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS v29.0 (IBM Corp., Armonk, NY, USA).

Results

Participant Characteristics

Out of 622 invited physicians, 200 completed both pre- and post-intervention surveys (response rate: 32.1%). The median participant age was 42 years (IQR: 38-47), and 49% were male. Most participants specialized in intensive care (63.5%) and worked primarily in intensive care units (71.5%). More than half (55.5%) had 6-15 years of clinical experience. A total of 53.5% reported that their institutions lacked a formal LAST protocol, while 19% were unsure of whether such a protocol existed.

According to Table 1, 42.5% of participants reported using LAs daily. A total of 51% had never encountered a case of LAST in their clinical practice. Additionally, 47% had never received formal training on the topic. The primary sources of LAST-related knowledge were medical education (38%), academic articles or books (34.5%), clinical experience (14.6%), and in-service training or seminars (12.7%).

Self-assessed Knowledge

Participants' self-ratings of their knowledge are shown in Table 2. The majority of participants rated their knowledge of clinical symptoms as good (38%) or moderate (31%), while 13% considered their knowledge to be very good. For LAST procedures, 28% selected "good" and 11% "very good" for their knowledge of clinical symptoms. Regarding LE therapy, 31% rated their knowledge as good and 11% as very good.

Effect of Educational Intervention

Following the intervention, participants showed significant improvements in several areas (Table 3).

Table 1. Demographic and professional experience regarding local anesthetic systemic toxicity

Variables	Total (n=200)	Total score (pre-education), median (IQR)	Total score (post-education), median (IQR)	p
Age, median (IQR)	42 (38-47)	-	-	-
Gender, n (%)				
Male	98 (49)	13 (11-13)	13 (12-14)	0.185
Female	102 (51)	12 (10-13)	13 (12-14)	
Clinical expertise, n (%)				
Intensive care medicine	127 (63.5)	12 (10-13)	13 (12-14)	0.012
Anesthesiology	73 (36.5)	12 (11-13)	13 (13-14)	
Department, n (%)				
Intensive care unit	143 (71.5)	12 (10-13)	13 (12-14)	0.064
Operating room	57 (28.5)	12 (11-13)	13 (12-14)	
Total professional experience in the specialty (years), n (%)				
0-5 years	62 (31)	12 (11-13)	13 (12-14)	0.748
6-10 years	72 (36)	12 (11-13)	13 (12-14)	
11-15 years	34 (17)	12 (10-13)	13 (12-14)	
≥16 years	32 (16)	12 (11-13)	13 (12-14)	
Is there a protocol in your institution for the management of LAST?, n (%)				
Yes	55 (27.5)	12 (11-13)	13 (12-14)	0.011
No	107 (53.5)	12 (10-13)	13 (12-14)	
I am not sure	38 (19)	12 (10-13)	13 (12-14)	
How often do you use local anesthetics?, n (%)				
Daily	85 (42.5)	12 (11-13)	13 (12-14)	
Weekly	62 (31)	11 (10-13)	13 (12-14)	0.105
Monthly	9 (4.5)	12 (10-13)	13 (12-14)	
Rarely	44 (22)	12 (11-13)	13 (12-14)	
How often do you encounter LAST cases?, n (%)				
I have never encountered	102 (51)	12 (11-13)	13 (12-14)	0.176
Rarely (1-2 times per year)	0 (0)	-	-	
Frequently (once a month or more)	98 (49)	12 (11-13)	13 (12-14)	
Have you ever received education on LAST management?, n (%)				0.070
Yes	106 (53)	12 (11-13)	13 (12-14)	
No	94 (47)	12 (11-13)	13 (12-14)	
What is your source of information regarding LAST management?, n (%)		-	-	-
Academic articles or books	130 (34.5)			
Learning during medical education	143 (38)			
Through experience	55 (14.6)			
In-service training or seminars	48 (12.7)			

IQR: Interquartile range, LAST: Local anesthetic systemic toxicity

Table 2. Self-assessment of knowledge and competence in the management of local anesthetic systemic toxicity among participants

Competency area	1 (I don't know at all)	2 (I know a little)	3 (Moderate)	4 (Good)	5 (Very good)
LAST procedures, n (%)	16 (8)	33 (16.5)	73 (36.5)	56 (28)	22 (11)
LAST clinical symptoms, n (%)	6 (3)	30 (15)	62 (31)	76 (38)	26 (13)
Lipid emulsion therapy in LAST, n (%)	15 (7.5)	36 (18)	65 (32.5)	62 (31)	22 (11)
Cardiovascular support in LAST, n (%)	10 (5)	25 (12.5)	65 (32.5)	76 (38)	24 (12)

LAST: Local anesthetic systemic toxicity

Table 3. Assessment of correct response rates for survey questions on local anesthetic systemic toxicity

Questions and answers	Pre-education (n=200) (%)	Post-education (n=200) (%)	p
Q1: What is the primary mechanism of local anesthetic systemic toxicity (LAST)? A: Blocking voltage-gated sodium channels.	130 (65)	124 (62)	0.302
Q2: What causes differences in the cardiotoxicity of local anesthetics? A: Protein binding capacities of drugs, pKa values of local anesthetics, lipophilic properties of local anesthetics.	151 (75.5)	165 (82.5)	0.055
Q3: Which local anesthetic application method carries the highest risk of LAST? A: Intravenous injection.	181 (90.5)	186 (93)	0.234
Q4: In which situation does topical local anesthetic use pose the highest toxicity risk? A: Application to mucosal surfaces.	23 (11.5)	21 (10.5)	0.437
Q5: Which of the following does NOT increase the risk of LAST? A: Intramuscular administration of local anesthetics.	139 (69.5)	193 (96.5)	<0.001
Q6: In which patient group is LAST risk higher? A: Patients with renal failure, pregnant women, elderly individuals.	191 (95.5)	198 (99)	0.031
Q7: Which of the following methods is not recommended for preventing LAST? A: Injection under deep sedation.	182 (91)	193 (96.5)	0.018
Q8: What method is recommended to ensure the safe administration of local anesthetics? A: Slow and gradual injection, aspiration control, use of epinephrine containing solution.	180 (90)	193 (96.5)	0.008
Q9: Which of the following is NOT an early sign of LAST? A: Urinary retention.	178 (89)	183 (91.5)	0.250
Q10: Which of the following is an advanced symptom of LAST? A: Ventricular arrhythmia, hypotension, respiratory depression.	192 (96)	190 (95)	0.405
Q11: What should be the first step in LAST management? A: Oxygen administration and airway protection.	175 (87.5)	190 (95)	0.006
Q12: Which antiarrhythmic drug should be preferred during LAST? A: Amiodarone.	150 (75)	191 (95.5)	<0.001
Q13: What should be the initial dose of lipid emulsion therapy (lipid rescue) for effective treatment in a patient weighing <70 kg? A: 1.5 mL/kg.	142 (71)	196 (98)	<0.001
Q14: Under what conditions should lipid emulsion infusion be discontinued? A: When cardiovascular stability is achieved, When seizures are completely controlled, after the maximum dose (12 mL/kg) is administered.	159 (79.5)	164 (82)	0.306
Q15: What is the primary mechanism of lipid emulsion therapy in LAST management? A: Removing the local anesthetic from toxic areas.	173 (86.5)	183 (91.5)	0.075

A: Answer, Q: Question, LAST: Local anesthetic systemic toxicity

Notably, understanding that intramuscular injection does not increase LAST risk improved significantly (Q5, p<0.001). Participants also demonstrated increased awareness of safe practices, including avoiding injection under deep sedation (Q7, p=0.018) and applying slow, incremental injection with aspiration and epinephrine use (Q8, p=0.008). LE-related knowledge also improved: correct identification of the initial LE dose (1.5 mL/kg) for patients <70 kg increased significantly (Q13, p<0.001).

Knowledge Score Changes

As shown in Table 4, the proportion of participants who answered all LE-related questions correctly (Q13-15) increased from 47% to 73.5% post-intervention (p<0.001). The total mean knowledge score improved from 11.7±1.7 to 12.8±1.2 (p<0.001). Before the intervention, 77% of participants were classified as having high knowledge levels, and 23% as moderate. After the intervention, 97% reached high knowledge levels, with only 3% remaining in the moderate group (p<0.001; Figure 1).

Regression Analysis

Multiple linear regression was used to identify predictors of baseline knowledge (Table 5). The model was significant [F (1,198)=4.921, p=0.028], with R^2=0.024 and adjusted R^2=0.019. Older age was associated with slightly lower scores (B=-0.035, 95% CI: -0.069 to -0.002, p=0.038). Anesthesiology specialization was a positive predictor (B=0.576, 95% CI: 0.065 to 1.087, p=0.027). Surprisingly, prior LAST training was associated with lower baseline scores (B=-0.554, 95% CI: -1.047 to -0.062, p=0.028).

Table 4. Comparison of the total number of participants with correct answers before and after training across survey question categories

Classification of questions	Pre-education (n=200) (%)	Post-education (n=200) (%)	p
LAST Mechanism (Q1 and 2)			
0	20 (10)	15 (7.5)	0.376
1	79 (39.5)	81 (40.5)	
2	101 (50.5)	104 (52)	
Pathophysiology of LAST (Q3 and 4)			
0	18 (9)	12 (6)	0.554
1	160 (80)	169 (84.5)	
2	22 (11)	19 (9.5)	
Epidemiology of LAST (Q5 and 6)			
0	6 (3)	2 (1)	<0.001
1	58 (29)	5 (2.5)	
2	136 (68)	193 (96.5)	
Risk factors and prevention of LAST (Q7 and 8)			
0	4 (2)	0 (0)	<0.001
1	30 (15)	14 (7)	
2	166 (83)	186 (93)	
Clinical manifestations of LAST (Q9 and 10)			
0	2 (1)	3 (1.5)	0.618
1	26 (13)	21 (10.5)	
2	172 (86)	176 (88)	
Management of LAST (Q11 and 12)			
0	8 (4)	2 (1)	<0.001
1	59 (29.5)	15 (7.5)	
2	133 (66.5)	183 (91.5)	
Lipid emulsion therapy (Q13, 14 and 15)			
0	2 (1)	0 (0)	<0.001
1	16 (8)	4 (2)	
2	88 (44)	49 (24.5)	
3	94 (47)	147 (73.5)	
Total score, mean ± SD	11.7±1.7	12.8±1.2	<0.001

Q: Question, LAST: Local anesthetic systemic toxicity, SD: Standard deviation

Table 5. Multiple linear regression analysis of factors influencing baseline knowledge scores

Predictor	B	95% CI	SE	t	p
Intercept	13.248	11.794 to 14.702	0.737	17.968	<0.001
Age	-0.035	-0.069 to -0.002	0.017	-2.089	0.038
Gender	-0.369	-0.865 to 0.126	0.251	-1.470	0.143
Female	-0.369	-0.865 to 0.126	0.251	-1.470	0.143
Male	Reference				
Specialty	0.576	0.065 to 1.087	0.259	2.224	0.027
Intensive care	Reference				
Anesthesia	0.576	0.065 to 1.087	0.259	2.224	0.027
Department	0.402	-0.147 to 0.951	0.278	1.445	0.150
ICU	Reference				
Operating room	0.402	-0.147 to 0.951	0.278	1.445	0.150
Experience	-0.024	-0.263 to 0.214	0.121	-0.200	0.841
Increasing experience	-0.024	-0.263 to 0.214	0.121	-0.200	0.841
Previous LAST training	-0.554	-1.047 to -0.062	0.250	-2.218	0.028
Yes	-0.554	-1.047 to -0.062	0.250	-2.218	0.028
No	Reference				

LAST: Local anesthetic systemic toxicity, CI: Confidence interval, ICU: Intensive care unit, SE: Standard error

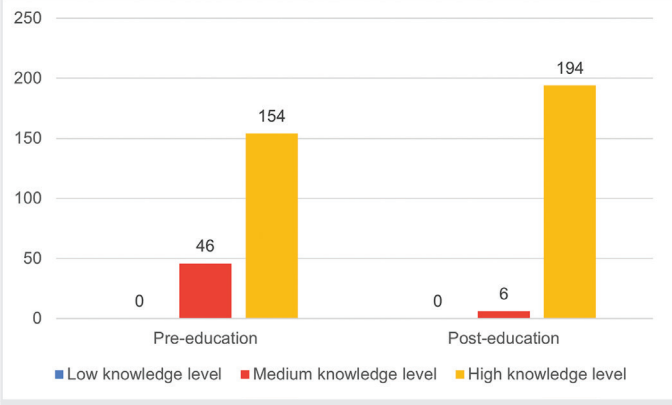

Figure 1. Comparison of total knowledge level group scores before and after education (p<0.001)

Discussion

This study evaluated the effectiveness of a brief educational intervention on improving anesthesiologists' and intensive care specialists' knowledge regarding LAST. The findings demonstrated a significant increase in objective knowledge scores following the intervention, particularly in areas such as management of LAST and the use of LE therapy. Although participants initially demonstrated moderate to high pre-education scores, the targeted education was effective in addressing their specific knowledge gaps.

In the current study, most anesthesiology and intensive care specialists rated their knowledge of LAST procedures, clinical symptoms, LE therapy, and cardiovascular support as moderate, good, or very good. These self-assessments are consistent with the findings of Rudra et al. (4), who reported high levels of confidence among anesthesiology trainees, particularly in areas such as prevention, risk factors, LE therapy, and site of administration. However, their study also revealed lower confidence in understanding the mechanism of LAST and in educational exposure, with a notable proportion of participants responding "neutral" or "disagree" to related items (4). Similarly, our study suggests that while general awareness of LAST among specialists is relatively positive, certain theoretical and training-related aspects remain insufficient. This discrepancy highlights the need for targeted educational interventions, especially in less emphasized areas like pathophysiology and structured instruction.

Our results align with previous national studies reporting suboptimal knowledge levels about LAST. In a study by Güler et al. (17), more than half of the participants had not received any training on LAs during their medical education, and only 22% were aware of the indications and use of LEs. Similarly, Karasu et al. (18) found that approximately two-thirds of physicians had never heard of LE therapy. Urfalıoğlu et al. (19) also reported that over 60% of ophthalmologists lacked knowledge about lipid use in LAST treatment. These findings collectively highlight the absence of standardized, comprehensive training on LAST across specialties.

Rudra et al. (4) reported that anesthesiology trainee physicians demonstrated a high level of knowledge regarding key aspects of LAST. Specifically, 100% correctly identified the contributing factors, 90% recognized the most common initial manifestation, 66% knew the timing of symptom onset, 87% identified the appropriate initial dose of LE therapy, and 83% were aware of the correct treatment

protocol (4). In contrast, participants in the present study showed lower levels of knowledge in these areas prior to the educational intervention. This discrepancy might be attributed to the fact that the participants in Rudra's study were still in training and likely had more recent exposure to LAST-related content. Meanwhile, the specialists in our study may have received such training earlier in their careers, with limited opportunities to refresh their knowledge due to infrequent clinical encounters with LAST. These findings emphasize the importance of continuous education and regular updates in clinical training.

The literature further supports the need for structured education programs. Munasinghe et al. (10) found that although 77% of Sri Lankan physicians claimed to have knowledge about LAST recognition and initial treatment, less than half correctly identified LE as the definitive therapy, and only two-thirds knew the correct dose. Similar to our findings, knowledge was significantly higher among anesthesiologists and postgraduate trainees compared to other physicians.

Similar to the findings of İlhan and Demir (13), the studies conducted by Karasu et al. (18) and Urfalıoğlu et al. (19) also demonstrated that most participants reported using LAs on a daily basis, yet the rates of formal training remained low, at 19.8% and 28.8%, respectively. Emergency physicians, who reportedly used LAs more frequently and had higher exposure to training, tended to answer LAST-related questions—such as symptoms, treatment, and LE dosage—more accurately. Despite the critical importance of education on LAST, İlhan and Demir (13) found no significant relationship between the frequency of LA use or prior training and the ability to correctly identify LAST symptoms, treatment strategies, or appropriate LE dosing. These findings suggest that the duration, quality, and content of existing LA-related training may be insufficient.

In the present study, participants who had previously received LAST training were found to have slightly lower total knowledge scores, possibly due to the extended time elapsed since their training and lack of regular clinical encounters with LAST. Karasu et al. (18) also reported that non-anesthesiology residents had lower rates of LAST education compared to anesthesiology trainees, a finding similarly reported by Sagir and Goyal (2), who documented limited knowledge and awareness among non-anesthesiology residents. Although İlhan and Demir (13) noted relatively higher training rates among emergency physicians, they still emphasized the inadequacy of overall educational exposure. In contrast, our study found that anesthesiology and intensive care specialists demonstrated comparatively acceptable levels of knowledge. Based on linear regression analysis, anesthesiologists appeared to have higher total knowledge scores, potentially due to their routine exposure to LAs in clinical practice. Interestingly, both increasing age and prior LAST training were negatively associated with total knowledge scores, further highlighting the need for continuous and updated educational initiatives in this field.

Numerous studies have highlighted insufficient knowledge of LAST among medical specialists, underlining the importance and necessity of targeted education (2,13,18). In the present study, both subjective self-assessments and objective test results indicated that anesthesiology and intensive care specialists had relatively high levels of knowledge regarding LAST. Nevertheless, gaps remained in certain fundamental areas, particularly concerning the underlying mechanisms of toxicity and prior educational exposure. These findings emphasize the need for structured and widespread educational programs to ensure safer clinical practice.

Previous literature has demonstrated the effectiveness of various training methods—ranging from live simulations to self-paced online modules—in enhancing knowledge and preparedness related to LAST (15,20,21). Consistent with these findings, our study showed that even a brief, targeted training intervention significantly improved participants' total knowledge scores, particularly in critical areas such as LAST management and the use of LE therapy.

Given that many participants reported the absence of a local protocol for LAST in their institutions, and nearly half indicated that they rarely encounter LAST cases or had never received prior formal education on the topic, the marked improvement observed after a short intervention highlights its potential impact. These results support the integration of routine, up-to-date, and accessible educational content on LAST within clinical training and continuing medical education programs.

Study Limitations

One of the main strengths of this study is its pre-post design, which allowed for a direct assessment of the impact of a brief educational intervention on knowledge levels regarding LAST among anesthesiology and intensive care specialists. Another strength of the study is the inclusion of a relatively large and well-defined sample of practicing specialists from multiple hospitals in İstanbul, which contributes to the generalizability of the findings. However, the final sample size was slightly below the initially estimated target. Additionally, the study provides valuable insights into the specific knowledge gaps and educational needs related to LAST, which can inform future training initiatives.

However, this study also has several limitations. First, data were collected through self-reported responses, which might be subject to recall and social desirability biases. Second, the study was limited to a single geographical region (İstanbul) and included only practicing specialists,

which might affect the external validity and generalizability of the findings. Third, the use of an online survey may have excluded participants less comfortable with digital tools, potentially introducing selection bias. Fourth, although the number of matched pre- and post-intervention responses (n=200) fell short of the estimated sample size based on a population of 1,000 professionals, post-hoc power analysis demonstrated adequate statistical power (1-β=0.999) for within-subject comparisons. Finally, the internal consistency of the knowledge questionnaire was relatively low (Cronbach's alpha=0.67), which might be attributed to the multidimensional content structure.

Conclusion

This study demonstrated that a brief, structured educational intervention significantly improved anesthesiology and intensive care specialists' knowledge of LAST, particularly in key areas such as clinical recognition, emergency management, and LE therapy. Although the majority of participants exhibited high baseline knowledge, the intervention effectively addressed specific knowledge gaps and underscored the importance of continuous education in rarely encountered but potentially life-threatening conditions such as LAST. The findings underscore the need to integrate LAST-focused content into specialty training curricula and continuing professional development programs. Establishing standardized institutional protocols and promoting regular refresher training may further enhance clinical preparedness and patient safety in settings where LAs are routinely administered.

Ethics

Ethics Committee Approval: The study received ethical approval from the Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (decision no: 170, date: 06.02.2025).

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

Footnotes

Authorship Contributions

Concept: A.G.K.K., Y.E.A., Design: A.G.K.K., Y.E.A., Data Collection or Processing: A.G.K.K., Analysis or Interpretation: Y.E.A., Literature Search: A.G.K.K., Y.E.A., Writing: A.G.K.K., Y.E.A.

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Original Article

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The Role of Uterine Artery Doppler Analysis in Predicting the Amount of Postpartum Hemorrhage in Cesarean Section

Sezaryende Postpartum Kanama Miktarını Öngörmede Uterin Arter Doppler Analizinin Yeri

Ecem ŞİMŞEK[1], Ramazan Erda PAY[3], Mehmet Bora BOZGEYİK[2], Mehmet Ferdi KINCI[2], Yaşam Kemal AKPAK[2]

[1]Ayvalık State Hospital, Clinic of Obstetrics and Gynecology, Balıkesir, Türkiye; AMEOS Hospital Group Holstein Ltd., Neustadt, Schleswig-Holstein, Germany
[2]University of Health Sciences Türkiye, İzmir City Hospital, Department of Obstetrics and Gynecology, İzmir, Türkiye
[3]University of Health Sciences Türkiye, Etlik City Hospital, Department of Obstetrics and Gynecology, Ankara, Türkiye

ABSTRACT

Objective: Postpartum hemorrhage (PPH) most commonly occurs within the first 24 hours after delivery. During this period, the uterus undergoes physiological involution, accompanied by hemodynamic changes that reduce uterine blood flow. This early postpartum phase represents a critical window in which uterine artery Doppler (UAD) indices begin to change but may not yet reach peak values. We hypothesized that Doppler measurements obtained during this period could provide early insight into susceptibility to blood loss. This study aimed to evaluate whether UAD parameters can predict hemoglobin (Hb) decrease in the early postpartum period.

Methods: A total of 56 low-risk pregnant women who underwent elective cesarean section were included. Bilateral UAD resistive index (RI) values were measured within the first 24 hours postpartum. Demographic characteristics and laboratory parameters were recorded. Mean UAD RI values were analyzed in relation to significant Hb decrease. Receiver operating characteristic analysis was performed to determine the optimal cut-off value of mean UAD RI associated with significant Hb decrease.

Results: The 75th percentile of Hb change was 0.938 g/dL and was defined as the threshold for significant Hb decrease. A

ÖZ

Amaç: Postpartum kanama (PPK) en sık doğumdan sonraki ilk 24 saat içinde ortaya çıkar. Bu dönemde uterus fizyolojik involüsyona uğrar ve uterin kan akımını azaltmaya yönelik hemodinamik değişiklikler meydana gelir. Bu erken postpartum dönem, uterin arter Doppler (UAD) indekslerinin değişmeye başladığı ancak henüz pik değerlere ulaşmadığı kritik bir zaman aralığını temsil eder. Bu çalışmada, bu dönemde yapılan Doppler ölçümlerinin kan kaybına yatkınlığı erken dönemde öngörmeye katkı sağlayabileceği hipotez edildi. Çalışmanın amacı, erken postpartum dönemde UAD parametrelerinin hemoglobin (Hb) düşüşünü öngörmedeki değerini değerlendirmektir.

Yöntem: Elektif sezaryen ile doğum yapan düşük riskli toplam 56 gebe çalışmaya dahil edildi. Doğum sonrası ilk 24 saat içinde bilateral UAD rezistif indeks (RI) değerleri ölçüldü. Demografik özellikler ve laboratuvar parametreleri kay-dedildi. Ortalama UAD RI değerleri ile anlamlı Hb düşüşü arasındaki ilişki analiz edildi. Anlamlı Hb düşüşü ile ilişkili ortalama UAD RI eşik değerini belirlemek amacıyla alıcı işletim karakteristiği eğrisi analizi yapıldı.

Bulgular: Hb değişiminin %75'lik persentil değeri 0,938 g/dL olarak bulundu ve bu değer anlamlı Hb düşüşü için eşik olarak kabul edildi. Ortalama UAD RI ≤0,915 olduğunda Hb düşüşü ile

Address for Correspondence: Ecem Şimşek MD, Ayvalık State Hospital, Clinic of Obstetrics and Gynecology, Balıkesir, Türkiye; AMEOS Hospital Group Holstein Ltd., Neustadt, Schleswig-Holstein, Germany
E-mail: dr.ecemsimsek@gmail.com
ORCID IDs of the authors: E.Ş.: 0009-0003-2562-8945, R.E.P.: 0000-0001-7183-4246, M.B.B.: 0000-0003-2169-0576, M.F.K.: 0000-0002-6798-4281, Y.K.A.: 0000-0002-1699-8667

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ABSTRACT

mean UAD RI value ≤0.915 was significantly associated with greater Hb decrease (p=0.025). A significant correlation was observed between mean UAD RI and preoperative Hb levels (r=-0.360, p=0.006). No significant correlation was found with other variables.

Conclusion: Monitoring mean UAD RI values in the early postpartum period may serve as a complementary clinical parameter for the early identification of PPH. While current evidence on postpartum UAD measurements remains limited, UAD indices appear to undergo dynamic changes within the first 24 hours in cases complicated by PPH. These findings suggest that UAD assessment may contribute to early risk stratification and support clinical decision-making; however, further large-scale studies are required to validate these results.

Keywords: Postpartum hemorrhage, uterine artery Doppler, hemoglobin, cesarean delivery

ÖZ

istatistiksel olarak anlamlı ilişki saptandı (p=0,025). Ortalama UAD RI ile preoperatif Hb düzeyleri arasında istatistiksel olarak anlamlı bir korelasyon bulundu (r=-0,360, p=0,006), diğer değişkenlerle anlamlı bir ilişki saptanmadı.

Sonuç: Erken postpartum dönemde ortalama UAD RI değerlerinin izlenmesi, PPK'nın erken tanımlanmasında tamamlayıcı bir klinik parametre olarak kullanılabilir. Postpartum dönemde UAD ölçümlerine ilişkin mevcut kanıtlar sınırlı olmakla birlikte, PPK ile komplike olgularda UAD indekslerinin ilk 24 saat içinde dinamik değişiklikler gösterdiği düşünülmektedir. Bu bulgular, UAD değerlendirmesinin erken risk sınıflandırmasına katkı sağlayabileceğini ve klinik karar verme süreçlerini destekleyebileceğini düşündürmektedir; ancak bu sonuçların doğrulanması için daha geniş ve çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Postpartum kanama, uterin arter Doppler, hemoglobin, sezaryen doğum

Introduction

Increased uterine contractions, placental separation, and reduced uterine blood supply after delivery are normal physiological processes. However, postpartum hemorrhage (PPH) that exceeds the expected physiological amount can progress rapidly, leading to maternal morbidity and mortality. While maternal mortality is a significant indicator of a country's level of development, it is often preventable with prompt intervention and treatment (1). Statistically, it has been revealed that PPH is observed in 1-5% of all pregnant women who give birth (2-4). PPH accounts for approximately 27% of maternal deaths each year. PPH is classified into two categories, primary and secondary, based on the timing of its occurrence. Primary PPH is the most common type. Generally, bleeding of more than 500 mL within the first 24 hours after a vaginal delivery, or more than 1000 mL within the first 24 hours after a cesarean delivery, is considered PPH (1). PPH is classified into two groups: minor and major bleeding. In this classification, minor PPH is defined as bleeding between 500 and 1000 mL, while major PPH is defined as bleeding of ≥1000 mL (1).

The uterine artery which is the main artery supplying the uterus, provides a blood flow of 500-700 mL per minute to the uterus, representing approximately 15% of the cardiac output on its own (5). Although uterine artery Doppler (UAD) measurements have been extensively studied obstetrically during the antenatal period, there is insufficient research on UAD measurements in the postpartum period, particularly during the first 24 hours when primary PPH is monitored. The literature indicates that notching can be observed in UAD during the first 8 weeks postpartum, with a 22% occurrence in the first week and a 95% occurrence between the 2nd and 8th weeks. Additionally, the UAD pulsatility index is approximately 1.2 in the first week but increases to >2 by the 8th week (6). In recent years, with the increase in cesarean section rates, it has become one of the most commonly performed surgeries worldwide (7,8). In our study, we aimed to correlate UAD measurements taken within the first 6 hours postpartum with preoperative and postpartum hemoglobin (Hb) levels changes in patients who delivered by cesarean section.

Postpartum hemodynamic shifts include a rapid reduction in uterine blood flow and increased vascular resistance as part of the physiological involution process. However, deviations from this normal pattern may reflect poor uterine contractility or abnormal placental bed remodeling-two important contributors to PPH. By assessing uterine artery resistive indices (RI) in the early hours postpartum, clinicians may detect insufficient vascular resistance increases that correlate with greater blood loss or Hb decrease. Our decision to perform UAD measurements at the 24 hours postpartum hour aimed to capture this transitional hemodynamic window, when both physiological and pathological changes are most pronounced and intervention can be most impactful. This novel approach aligns with limited but emerging literature suggesting the utility of postpartum Doppler evaluation in hemorrhage prediction.

Through this study, we aimed to predict Hb level changes during the postpartum period using UAD measurements.

Methods

Our study is designed as a prospective cohort study. Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İzmir City Hospital (decision no: 2024/57, date: 10.05.2024). This study was conducted in compliance with the Helsinki Declaration and informed consent was obtained from all participants before starting the study.

Patient Selection

Between May 10, 2023, and June 1, 2024, 56 pregnant women who met the inclusion criteria and had no additional diseases or characteristics were included in the study at University of Health Sciences Türkiye, İzmir City Hospital, whom delivered via elective or emergency cesarean section. Bilateral UAD measurements were performed using postpartum pelvic Doppler ultrasound. For this, a GE Voluson Ultrasound Machine (GE Healthcare, Milwaukee, Wisconsin, USA) with a Convex 4C-RS (2-5 MHz) probe was used. Hemogram parameters from the last 24 hours before delivery and hemogram values at the 24th hour postpartum were collected. Data related to delivery, as well as Hb, white blood cell (WBC), and platelet (PLT) values, were recorded.

Inclusion Criteria

Pregnancies beyond 37 weeks and less than 41 weeks of gestation, women aged 18 to 40 years, patients with a body mass index (BMI) under 35 kg/m², those who did not progress to the active phase of labor before cesarean section, those without any vascular conditions such as vasculopathy or autoimmunity affecting the vascular bed, those without coagulopathy or anticoagulant therapy, those without injuries that could cause additional blood loss, those without intense bleeding from the wound site postpartum, those without placental anomalies, and those who were willing to participate in the study.

Exclusion Criteria

<37 weeks gestation and >41 weeks gestation, women under 18 years of age and over 40 years of age, patients with a BMI >35 kg/m², patients in the active phase of labor, pregnant women with vascular conditions such as vasculopathy or autoimmunity affecting the vascular bed, those with coagulopathy or receiving anticoagulant therapy, those with injuries that could cause additional blood loss, patients with placental anomalies such as previa, accreta, placental abruption, intrauterine growth restriction or other conditions known to alter uterine hemodynamics, postpartum patients with intense bleeding from the wound site, patients with detected placental anomalies, those unwilling to participate in the study, and those with four or more previous cesarean sections.

Surgical Technique

Spinal anesthesia was administered to the patients according to the procedure. After the abdominal layers were dissected according to the Pfannenstiel incision technique, the baby was delivered through a Kerr incision. Following the removal of the placenta, intrauterine cleaning was performed. A Kehr suture was applied. Bleeding was controlled, and the abdominal layers were closed according to standard procedures (8).

Patients with stable hemodynamics after cesarean delivery were monitored in our clinic. Hourly vital signs were tracked. Infusion of a 2% oxytocin Ringer's lactate solution was continued for approximately 4 hours. Routine analgesia and IV hydration treatments were administered postpartum. If there was no bleeding and the uterine tone was good, the uterotonic infusion was discontinued. Breastfeeding and uterine massage were encouraged. Routine hemogram checks were performed at the 24th hour postpartum. The results were recorded.

Uterine Artery Doppler Measurement

Patients were subjected to ultrasound examination in the supine position at 24 hours after cesarean operation, once their hemodynamics were stable. The uterus was examined in the midsagittal position. The cervical canal was identified, and the iliac and uterine arteries were visualized using Doppler flow mapping. Doppler measurements were performed at least twice for each uterine artery, 1 cm distal to the point where the uterine artery crosses the external iliac artery, capturing at least three consecutive waveforms. Average values were recorded.

Based on the uterine artery diameter, the sample volume size was adjusted, and measurements were taken with an insonation angle of <25°. All ultrasound and Doppler evaluations were conducted by a single researcher (E.Ş.). All measurements were recorded for further analysis. UAD ultrasound measurements were recorded for both the right and left uterine arteries, and the average values were calculated (9).

Statistical Analysis

Sample size was calculated using G*Power software (version 3.0.10). With a type I error level of α=0.05 and a power of 80% (1-β=0.80), the required sample size was determined to be 56 participants. Statistical analyses were performed using IBM SPSS Statistics (version 17.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were presented as mean ± standard deviation for normally distributed data and as median (minimum-maximum) for non-normally distributed data. The distribution of postpartum Hb change was analyzed, and the 75th percentile (fourth quartile) was used as the cut-off value to define significant Hb decrease. Comparisons between two independent groups were performed using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. For comparisons among more than two independent groups, one-way analysis of variance or the Kruskal-Wallis test was used, as appropriate. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test when necessary. Correlation analysis between continuous variables was performed using Pearson or Spearman correlation coefficients, depending on data distribution. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the ability of mean UAD RI values to predict postpartum Hb change.

The area under the curve (AUC), optimal cut-off values, sensitivity, and specificity were determined. A p-value of <0.05 was considered statistically significant. Bonferroni correction was applied where appropriate to adjust for multiple comparisons.

Results

The age, preoperative and postoperative WBC, Hb, PLT, estimated fetal weight (EFW), left and right UAD systolic/diastolic flow ratios, right and left UAD RI, and the mean UAD RI measurements of the participants included in the study are listed in Table 1. In our study, we primarily tried to evaluate the usefulness of UAD indices in the prediction of PPH. Therefore, the relationship between UAD RI (mean) and Hb changes (difference between post-Hb and pre-Hb) was evaluated. The 4th quartile (75% percentile) value for Hb level change was 0.938 g/dL. Accordingly, a Hb level change of ≥0.938 g/dL measurements obtained at the 24th hour postpartum were considered as a significant Hb decrease and subsequently used as a criterion for PPH. The percentile data of Hb changes of the patients are presented in Table 2. An ROC curve was constructed for the continuous variable of mean UAD RI, which was found to be associated with a significant Hb decrease (Figure 1). The area under the AUC was determined to be 0.674 [(95%) confidence interval (CI): 0.531-0.818] (p=0.027).

In the AUC, appropriate cut-off values with the highest sensitivity and specificity were determined. The risk of PPH appeared to increase when UAD RI (mean) ≤0.915. Furthermore, the distribution of patients with a significant decrease in Hb when UAD RI (mean) was taken as 0.915 is shown in Table 3. When the data of 56 patients were analyzed in total, a significant Hb decrease (≥0.938 g/dL) was observed in 20 of 36 patients (55.55%) with UAD RI (mean) ≤0.915, whereas a significant hemogram decrease (≥0.9387 g/dL) was observed in 4 of 20 patients (20%) with UAD RI (mean) >0.915. Accordingly, statistical significance of significant Hb level decrease was achieved when UAD RI (mean) ≤0.915 (p=0.025) (Table 3).

An AUC was constructed for age, a continuous variable found to be associated with a significant decrease in Hb (Figure 2). The area under the AUC was 0.768 (95% CI: 0.636-0.901) (p=0.001). This indicated that the risk of bleeding increased when the age threshold was set at 24.5 years (p=0.001) (Table 4).

The statistical correlation between preoperative WBC, preoperative Hb values and mean RI values are summarized in Table 5.

The correlation between groups with and without significant Hb decrease and the continuous variables was analyzed. The variables showing statistically significant differences were age and mean RI values (p<0.05). These findings are summarized in Table 6.

Table 1. Descriptive statistical analysis of continuous variables

Continuous variables	Min. value	Max. value	Mean	SD
Age (year)	19.0	33.0	26.60	4.474
Preoperative WBC (/µL)	7230.0	18720.0	12137.85	2465.07
Postoperative WBC (/µL)	10300.0	20580.0	14238.21	2605.72
Preoperative Hb (g/dL)	7.4	13.6	11.73	1.43
Postoperative Hb (g/dL)	8.2	13.3	10.70	1.34
Preoperative PLT (/µL)	128000.0	377000.0	249892.85	61580.0
Postoperative PLT (/µL)	111000.0	360000.0	217321.42	55849.8
EFW (gr)	2100.0	4370.0	3101.42	591.42
Left UAD S/D	1.9600	10.0	5.227	1.851
Right UAD S/D	2.1000	7.36	4.726	1.337
Mean systolic/diastolic ratio of the right and left UAD (S/D)	2.1	7.5	4.977	1.231
Left UAD RI	0.54	1.48	0.914	0.223
Right UAD RI	0.57	1.39	0.916	0.204
Mean UAD RI	0.695	1.38	0.915	0.190

S/D: Systolic/diastolic flow ratio, RI: Resistive index, WBC: White blood cell, Hb: Hemoglobin, SD: Standard deviation, PLT: Platelet; EFW: Estimated fetal weight, UAD: Uterine artery Doppler

Table 2. Percentile data of postpartum hemoglobin (Hb) change

	%25	%50	%75
Hb change (g/dL)	0.80	0.84	0.938

When the Spearman's rho correlation analysis between mean UAD RI value and Hb level change and continuous variables was analyzed, it was found that age was negatively correlated with Hb change (r=-0.438, p=0.001) (p<0.05), negative between mean RI and gravida (r=-0.322, p=0.016), negative between mean RI and parity (r=-0.350, p=0.008), positive between mean RI and EFW (r=0.322, p=0.0016) (p<0.05). The results are summarized in Table 7.

Discussion

PPH is a significant condition that often arises acutely due to unpredictable causes during the postpartum period and can lead to maternal morbidity and mortality. Predicting and preventing this condition is crucial for preventing maternal mortality and morbidity (10). In the literature, UAD analysis has been studied in relation to menstrual cycles, healthy pregnancy monitoring during the intrapartum period, high-risk pregnancy monitoring during the intrapartum period, and throughout both the intrapartum and postpartum processes (9,11). However, studies using UAD analysis during the postpartum period are limited. In this study, we aimed to predict the amount of bleeding by measuring UAD resistances at the 24th hour postpartum.

In multiparous women, decreased UAD RI values were observed compared to primiparous women. In a study conducted by Guedes-Martins et al. (5), it was found that multiparous women had lower UAD RI values in the early postpartum period compared to primiparous women. This study is highly similar to ours in that it evaluates PPH

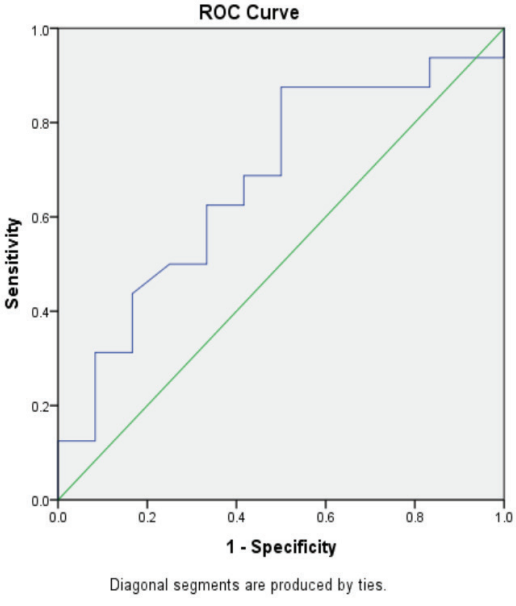

Figure 1. ROC analysis for mean UAD RI value in relation to significant Hb decrease

ROC: Receiver operating characteristic, UAD: Uterine artery Doppler, RI: Resistive index, Hb: Hemoglobin

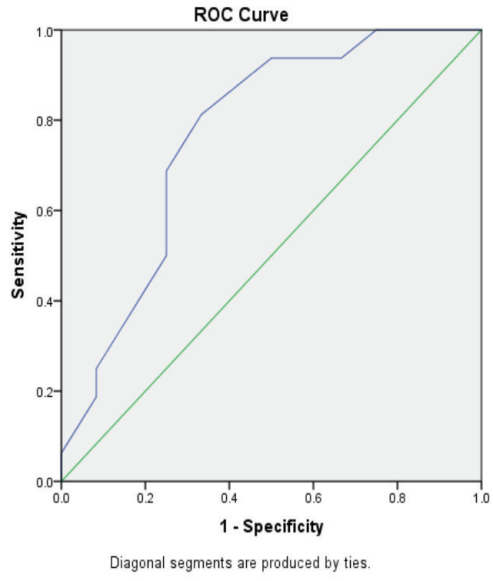

Figure 2. ROC analysis for significant Hb change and age continuous variable

ROC: Receiver operating characteristic, Hb: Hemoglobin

Table 3. Distribution of significant Hb decrease in patients when the cut-off value for UAD RI (mean) is chosen as 0.915

UAD RI (mean)				
Significant Hb decrease (≥0.938 g/dL)	**≤0.915**	**>0.915**	**Total**	**p**
Absent	16	16	32	
Present	20	4	24	
Total	36	20	56	**0.025**

UAD: Uterine artery Doppler, RI: Resistive index, Hb: Hemoglobin, RI: Resistive index

Table 4. Distribution of significant Hb decrease among patients based on age (cut-off 24.5 years)

Age (year)				
Significant Hb decrease (≥0.938 g/dL)	**≤24.5**	**>24.5**	**Total**	**p**
Absent	12	20	32	
Present	14	10	24	
Total	26	30	56	**0.021**

Hb: Hemoglobin

Table 5. Average RI value and correlation analysis of variables correlation analysis

Spearman's rho	Preoperative WBC (/μL)	r	-0.241
		p	0.074
	Preoperative Hb (g/dL)	r	-0.360
		p	**0.006**

r: Correlation coefficient p: Significance level p<0.05 is shown in bold with statistically significant data, WBC: White blood cell, RI: Resistive index, Hb: Hemoglobin

in women who deliver by cesarean section. In the study conducted by Diniz et al. (11), uterine blood flow was assessed with two ultrasound examinations, one within the first 48 hours and the other between the 31st and 50th days. According to this study, a lower increase in UAD RI was recorded in multiparous women compared to primiparous women (11). The underlying reason for this finding is most likely the recorded uterine artery regenerations that occurred in previous pregnancies of multiparous women. The remaining regenerations in the uterine artery affect subsequent pregnancies.

In our study, we found that women aged 19-24.5 had a higher tendency towards PPH. In this group, UAD RI values were below 0.915, and Hb level decrease was above 0.938 g/dL. According to the literature, Cleary-Goldman et al. (12) compared postpartum complications of cesarean deliveries between women aged 18-24 and those aged 35 and older. They reported that women aged 18-24 undergoing cesarean delivery had an increased risk of PPH and a higher need for blood transfusion (12). It has been shown to increase neonatal complications in women of advanced maternal age and maternal complications in women aged 18-24 years in the reproductive period. In another study by Lao et al. (13) evaluating the correlation between PPH and maternal age, it was reported that the risk of PPH decreased from the 20-24 age group to the >40 age group. In this study, the adjusted odds ratio for PPH was 0.84 in the 25-29 age range, and a progessive decrease was observed, reaching 0.59 in women aged 40 and over. In a study conducted by Hessler et al. (14), age-related vascular changes in uterine arteries were demonstrated, with calcific lesions present in 0% of women aged 45-49 years, increasing to 3.9% in the 50-59 age group, 37% in the 60-69 age group, and reaching 50% in women aged 70-81 years. It can be understood that the decreasing uterine blood flow index with aging may play a protective role against PPH. In our study, postpartum UAD RI values were found to be higher in women who delivered macrosomic babies (>4000 g) compared to those who delivered babies of normal weight. In contrast, the study by Guedes-Martins et al. (5) did not report a significant effect of infant birth weight. In this study, while the timing of data collection was not standardized, UAD measurements were conducted no earlier than one week postpartum. Our study measured UAD at the 24th hour, and the data were recorded. We found that early UAD analysis did not increase the risk of PPH following cesarean delivery of a macrosomic baby. This is probably due to the fact that the pregnant women with a birth weight of 4000 g and above in our study population were 30 years of age and older and were primiparous. In these pregnant women who did not have additional defining risk factors, a low severity positive RI correlation was observed according to our study results. It would be useful to evaluate the presence of a macrosomic baby, which is considered among the risk factors for PPH, with other defining risk factors. It is a normal physiological finding that uterine artery resistance has low values in UAD records during a healthy pregnancy, as this low resistance helps provide the necessary blood flow to the uterus. In the postpartum period, an increase in uterine artery resistance is expected due to the reduced blood supply to the uterus. This physiological change helps mitigate the risk of PPH (5). In this study, a decrease in UAD resistance index values and an increase in uterine artery resistance were observed in the postpartum uterus, which can be seen as a natural physiological consequence of the physiological cascade. We aimed to determine the correlation between UAD resistance and the change in Hb levels by comparing the values before cesarean delivery and at the 24th hour postpartum. Since there is no specific Hb level change laboratory value defined for PPH in the literature, we used laboratory data from our population to define PPH. According to this distribution, the reference threshold for PPH was estimated at the 4th quartile (75th percentile), with an average blood loss (Hb) of 0.938 g/dL. A decrease in Hb of 0.938 g/dL or higher was selected as the indicator for PPH. In our study, other factors that we selected as potentially affecting blood loss were also evaluated (gravida, parity, birth weight, age, PLT, WBC). The correlation between the variable created for Hb change and the mean UAD RI value was tested separately. The correlations of the variables with Hb change and the mean UAD RI value were tested separately. While the mean UAD RI value showed a correlation with four parameters, Hb level change was only correlated with maternal age. In our study, we believe that the mean UAD RI value could be a more sensitive parameter

Table 6. Correlation analysis between significant hemoglobin decrease and continuous variables

	Hb decrease >0.938 g/dL		Hb decrease <0.938 g/dL		
	Mean	**± SD**	**Mean**	**± SD**	**p**
Age (year)	25.5	3.94	28.5	4.52	**0.001**
Mean UAD RI	0.908	0.21	0.932	0.19	**0.022**

SD: Standard deviation, Hb: Hemoglobin, UAD: Uterine artery Doppler, RI: Resistive index

Table 7. Correlation analysis between the mean UAD RI value, Hb change, and continuous variables

		Mean RI	Hb change (g/dL)
Age (year)	r	-0.109	-0.438
	p	0.426	0.001
Gravida (n)	r	-0.322	0.072
	p	0.016	0.598
Parity (n)	r	-0.350	0.026
	p	0.008	0.850
EFW (gr)	r	0.322	0.187
	p	0.0016	0.168

r: Correlation coefficient, p: Significance level, UAD: Uterine artery Doppler, RI: Resistive index, Hb: Hemoglobin, EFW: Estimated fetal weight

for the early detection of PPH. What distinguishes our study from the limited similar studies in the literature is the correlation between Hb level change and the average RI value for each variable. Our ROC analysis of age groups, average RI, and Hb level change groups revealed a strong correlation with high CIs.

Study Limitations

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the statistical power of the findings. Second, the absence of a clearly defined PPH cohort restricts the ability to draw definitive conclusions regarding predictive performance. Third, the single-center design may limit the generalizability of the results to broader populations. In addition, the timing of Doppler measurements was limited to a single postpartum time point, which may not fully capture the dynamic changes in uterine artery hemodynamics. Therefore, the findings should be interpreted with caution, and further large-scale, multicenter studies are warranted to validate these results.

Conclusion

Monitoring mean UAD RI values in the early postpartum period may serve as a complementary clinical parameter for the early identification of PPH. These findings suggest that UAD assessment may provide additional support in early risk stratification and clinical decision-making when interpreted together with clinical and laboratory parameters. However, given the limitations of the study, these results should be interpreted with caution, and further large-scale, multicenter studies are needed to confirm these findings.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İzmir City Hospital (decision no: 2024/57, date: 10.05.2024).

Informed Consent: This study was conducted in compliance with the Helsinki Declaration and informed consent was obtained from all participants before starting the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.Ş., M.F.K., Concept: E.Ş., R.E.P., Design: E.Ş., M.B.B., Data Collection or Processing: E.Ş., M.B.B., Analysis or Interpretation: R.E.P., Y.K.A., Literature Search: E.Ş., Y.K.A., Writing: E.Ş., M.F.K.

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Original Article

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Role of Prothrombin Complex Concentrates in Reversal of Direct Oral Anticoagulant Effects

Yeni Nesil Oral Antikoagülan Etkilerinin Tersine Çevrilmesinde Protrombin Kompleksi Konsantrelerinin Rolü

Gökhan ERSUNAN[1], İsmail ATAŞ[1], Mümin Murat YAZICI[1], Enes GÜLER[2], Özlem BİLİR[1]

[1]Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye
[2]Kırklareli University Training and Research Hospital, Department of Emergency Medicine, Kırklareli, Türkiye

ABSTRACT

Objective: The aim of this study is to evaluate the efficacy and safety of four-factor prothrombin complex concentrate in reversing the anticoagulant effect in patients presenting to the emergency department with bleeding associated with direct oral anticoagulants.

Methods: This single-center, retrospective study evaluated the dosage and efficacy of prothrombin complex concentrate in reversing the anticoagulant effect in patients presenting to the emergency department of a tertiary hospital due to bleeding associated with direct oral anticoagulants or due to elevated international normalized ratio prior to an emergency procedural intervention associated with direct oral anticoagulants.

Results: Of the 20 participants, 65% were 80 years of age or older. The most common presenting complaints were gastrointestinal and musculoskeletal bleeding. The participants received a total of 34 doses (500 IU/20 mL) of prothrombin complex concentrate, and pre- and post-treatment coagulation test results showed significant improvement. However, no significant relationship was observed between hospital outcome (i.e., death or discharge) and the treatment protocols. Four patients developed thromboembolic events after treatment, and two of these had received more than one prothrombin complex concentrate dose.

Conclusion: Four-factor prothrombin complex concentrates are useful adjuncts for the urgent reversal of the direct oral anticoagulants-associated anticoagulant effects, particularly

ÖZ

Amaç: Bu çalışmanın amacı, yeni nesil oral antikoagülanlara bağlı kanamalarda dört faktörlü protrombin kompleks konsantresinin acil servisteki hastalarda antikoagülan etkisini tersine çevirmedeki etkinliğini ve güvenliğini değerlendirmektir.

Yöntemler: Bu tek merkezli, retrospektif çalışma, yeni nesil oral antikoagülanlarla ilişkili kanama nedeniyle veya yeni nesil oral antikoagülanlarla ilişkili acil prosedürel işlem öncesi uluslararası normalleştirilmiş oran yüksekliği saptanması üzerine üçüncü basamak bir hastanenin acil servisine başvuran hastalarda protrombin kompleks konsantresinin antikoagülan etkisini tersine çevirmedeki dozajını ve etkinliğini değerlendirmiştir.

Bulgular: Yirmi katılımcının %65'i 80 yaş ve üzerindeydi. En sık görülen şikayetler gastrointestinal ve kas-iskelet sistemi kanamalarıydı. Katılımcılara toplam 34 doz (500 IU/20 mL) protrombin kompleks konsantresi verildi ve tedavi öncesi ve sonrası pıhtılaşma testi sonuçları önemli bir iyileşme gösterdi. Ancak, hastane sonlanımı (yani ölüm veya taburculuk) ile tedavi protokolleri arasında önemli bir ilişki gözlenmedi. Dört hastada tedaviden sonra tromboembolik olay gelişti ve bunlardan ikisi birden fazla protrombin kompleks konsantresi dozu almıştı.

Sonuç: Dört faktörlü protrombin kompleks konsantreleri, özellikle bu tür müdahalelere ihtiyaç duyanların çoğunluğunu oluşturan geriatrik hastalarda, yeni nesil oral antikoagülanlarla ilişkili antikoagülan etkilerin acil olarak tersine çevrilmesi için

Address for Correspondence: İsmail Ataş MD, Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye
E-mail: drismailatas@gmail.com
ORCID IDs of the authors: G.E.: 0000-0002-4523-0294, İ.A.: 0000-0001-6723-8564, M.M.Y.: 0000-0003-1957-7283, E.G.: 0000-0003-4926-0332, Ö.B.: 0000-0001-9016-1665

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ABSTRACT

in geriatric patients who comprise the majority of those requiring such interventions. Nonetheless, clinicians should be aware that the risk of thromboembolism may increase with repeated dosing.

Keywords: Factor Xa inhibitors, direct thrombin inhibitors, anticoagulant reversal

ÖZ

yararlı yardımcı maddelerdir. Bununla birlikte, klinisyenler tekrarlanan dozlarla tromboemboli riskinin artabileceğini bilmelidir.

Anahtar Kelimeler: Faktör Xa inhibitörleri, doğrudan trombin inhibitörü, antikoagülan tersine çevirme

Introduction

Anticoagulants are a group of drugs with a wide range of indications, including atrial fibrillation, venous thromboembolism, and thromboprophylaxis, in patients at risk of thrombosis (1). The use of direct thrombin inhibitors, such as dabigatran, or direct factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban, has become preferable due to problems in coagulation monitoring and dose adjustment as well as the drug-drug and diet-drug interactions of vitamin K antagonists, such as warfarin (2). Compared with warfarin, the new generation of oral anticoagulants has a lower risk of life-threatening bleeding (3). Unlike vitamin K antagonists, direct oral anticoagulants (DOAC) do not require monitoring. Nonetheless, patients should be informed of conditions that may pose a bleeding risk as well as the signs and symptoms of bleeding. In particular, the use of drugs that predispose patients to bleeding, such as drugs used to treat uncontrolled systemic hypertension (systolic blood pressure >160 mmHg), drugs used to treat impaired renal function, antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAID), and selective serotonin reuptake inhibitors (SSRI), should be restricted (4).

Appropriate strategies must be established to prevent bleeding due to anticoagulation and to manage bleeding in the event of bleeding. To determine a treatment, it is important to understand the severity and extent of the bleeding. Bleeding that is mostly self-limiting, such as epistaxis, ecchymosis, mucosal bleeding, menorrhagia, and hematuria, is classified as mild bleeding. Bleeding that requires hemodynamic support related to the upper and lower gastrointestinal (GI), respiratory, or urogenital systems but does not require a transfusion and is not associated with anemia is classified as moderate bleeding. Bleeding in critical regions or organs (e.g., intracranial, intraspinal, intraocular, retroperitoneal, pericardial bleeding) is classified as symptomatic major bleeding (5).

Specific antidotes, such as idarucizumab or andexanet alfa, or non-specific agents, such as prothrombin complex concentrate (PCC) or recombinant factor VIIa (rFVIIa), may be used to reverse anticoagulation in patients using DOACs (6). However, it is not always possible to obtain a supply of specific antidotes or rFVIIa. Therefore, emergency departments may use PCC in cases of life-threatening or moderate bleeding or when an urgent procedural intervention is required. This study aimed to evaluate the effectiveness and safety of PCC in patients using DOACs who presented either with major bleeding or required urgent procedural or surgical intervention necessitating reversal of anticoagulation in the emergency department.

Methods

Study Design

This retrospective review investigated the dosage and efficacy of PCC for the reversal of anticoagulation in patients admitted to the emergency department of a tertiary hospital between May 2022 and October 2024 for bleeding associated with DOAC use. Approval was obtained from the Local Ethics Committee of Recep Tayyip Erdoğan University before the study commenced (decision no: 2025/244, date: 02.06.2025). Furthermore, this study was conducted in accordance with the Declaration of Helsinki.

Study Population and Variables

Patients who fit the inclusion criteria were identified by searching the hospital information management system (HIMS). The inclusion criteria were (1) patients over 18 years of age who presented to the emergency department with an international normalized ratio (INR) value >1.5 and were using DOACs, and (2) patients who used DOACs and either experienced life-threatening intracranial, GI, or intra-abdominal bleeding, or required an urgent procedural or surgical intervention, even in the absence of active bleeding, for which pre-procedural reversal of anticoagulation was indicated. For the latter group, PCC was administered to lower the INR to <1.5, in accordance with perioperative anticoagulation recommendations stating that invasive procedures should ideally be performed when coagulation parameters are normalized or INR is below 1.5 (7). The exclusion criteria were (1) patients under 18 years of age; (2) patients with clinical symptoms or laboratory tests indicative of disseminated intravascular coagulation; (3) patients with a known congenital protein C, protein S, or antithrombin deficiency or a hereditary bleeding disorder; (4) patients with acute or chronic liver failure or renal failure or those on dialysis; and (5) patients who received fresh frozen plasma prior to PCC administration.

Data were obtained from HIMS and emergency department patient registration files. Specifically, data were collected

on demographic information (age, gender, comorbid diseases, drugs used to treat the diseases, the anticoagulant used, and the reason for its use), complaint at presentation, reason for the reversal of the anticoagulant effect, the coagulation parameters before and after treatment, the laboratory parameters for the renal and liver function test results, the treatment administered and the dose, the outcome in the emergency department, whether there was a need for inpatient follow-up and treatment, the number of days of follow-up, and the follow-up clinic.

Thromboembolic events were monitored throughout hospitalization and up to 30 days following PCC administration. Events were identified through clinical evaluation, laboratory findings (including elevated troponin or D-dimer values when available), and confirmatory imaging such as computed tomography (CT) angiography, brain CT/magnetic resonance imaging, or Doppler ultrasonography when clinically indicated. Documentation from outpatient follow-up visits and electronic hospital records was also reviewed to identify delayed thromboembolic events. Only clinically confirmed events were included in the analysis.

Treatment Protocols and Guidelines

The Turkish Medicines and Medical Devices Agency, which is affiliated with the Turkish Ministry of Health, defined the indications and dosing requirements for the use of four-factor PCC in patients with life-threatening bleeding to reverse anticoagulation (8). The dose is adjusted based on pretreatment INR, target INR, and body weight. In our study, patients received PCC or PCC plus vitamin K to reverse the anticoagulant effect. PCC use in the emergency department was based on weight, INR, and life-threatening conditions caused by coagulopathy.

Similarly, in a multicenter observational cohort by Singer et al. (9), which examined factor Xa inhibitor-associated intracranial and GI bleeding, a considerable proportion of patients presented with INR >1.5 or prolonged prothrombin time (PT) values and still received PCC for hemostatic reversal. This finding supports the clinical rationale for including patients with INR >1.5 and active bleeding or procedural indications in the current study population (9). In our institution, four-factor PCC is supplied and authorized under a national and local protocol that recommends its use in patients with coagulopathy and an INR value >1.5 in the setting of major bleeding or prior to urgent invasive procedures. Although INR is not a specific or sensitive measure of DOAC activity, this threshold is used as a pragmatic laboratory trigger to support clinical decision-making in the emergency department. Accordingly, in this retrospective study INR >1.5 was adopted as an inclusion criterion and as a marker of coagulopathy at presentation, in combination with a documented history of DOAC use and either active bleeding or the need for urgent procedural or surgical intervention.

Guidelines published by the European Society of Anaesthesiology and Intensive Care and the Thrombosis and Haemostasis Society of Australia and New Zealand offer recommendations for the management of patients presenting to an emergency department due to bleeding related to DOACs (6,10). The anticoagulant agent is temporarily discontinued, and then the patient's hemoglobin level is evaluated to determine the severity of the bleeding. Standard coagulation tests and liver and kidney function tests are ordered to determine the effect of the agent on the current clinical picture. General supportive care measures are provided to identify the source of the bleeding and limit ongoing bleeding. The use of PCC is considered in cases of major, life-threatening bleeding or for patients scheduled to undergo surgical procedures. If dabigatran is used as an oral anticoagulant, hemodialysis may be used as the last resort when idarucizumab is generally unavailable and PCC is ineffective.

Primary and Secondary Endpoints

The primary endpoint of this study was the change in coagulation parameters [PT, activated partial thromboplastin time (aPTT), and INR values] from baseline to within the first six hours after PCC administration. Secondary endpoints included all-cause in-hospital mortality, the occurrence of thromboembolic events within 30 days (including myocardial infarction, ischemic stroke, pulmonary embolism, or deep venous thrombosis), emergency department outcome (discharge, ward admission, or ICU admission), and total length of hospital stay. Additionally, changes in laboratory values at 48 hours after PCC administration were recorded to support treatment response assessment.

Statistical Analysis

All analyses were performed using Jamovi v.1.6 statistical software (The Jamovi Project, Sydney, Australia). Categorical data were expressed in frequency (n) and percentage. Normally distributed continuous variable data were described as mean plus standard deviation (SD), and non-normally distributed data as median and interquartile range (IQR). The normality of distribution was evaluated using the Shapiro-Wilk test. The t-test/paired t-test was applied in the comparison of continuous variables in the case of normal distribution, and the Mann-Whitney U/Wilcoxon test in the case of non-normal distribution. The chi-square test was used to compare categorical variables between the groups. In all statistical analyses, $p<0.05$ was considered significant.

Results

During the study period, 34 doses of four-factor PCC were administered to 20 patients. Regarding demographics, 65% of the patients were female, and the mean age was 81.00±14.30 (mean ± SD). The most commonly used anticoagulant agent was rivaroxaban (65%, n=13). In 75% of cases, an anticoagulant was used due to atrial fibrillation. The reason for presentation to the emergency

department was bruising in 25% of cases, confusion in 15%, and hematuria in 10%. In 35% of cases, after evaluation of patients, GI bleeding was the most common type of bleeding. A subset of patients (n=4; 20%) received PCC despite the absence of active bleeding because urgent procedural or surgical intervention was required. Therefore, these patients were not assigned a bleeding severity category and were instead classified separately as "no active bleeding (procedural indication)" Table 1 shows the demographic data of the patients. The most common risk factors increasing patients' susceptibility to bleeding due to DOAC use were renal dysfunction (40%, n=8), NSAID use (20%, n=4), aspirin (15%, n=3), and SSRI use (10%, n=2).

The median time to improvement in the coagulation parameters was 4.65 (IQR: 3.00-6.47) hours. There were statistically significant decreases in PT, aPTT, and INR immediately after treatment compared to pretreatment (p=0.001, p=0.003, p=0.001, respectively). Similarly, PT, aPTT, and INR were statistically lower 48 hours after treatment compared to pretreatment (p=0.001, p=0.001, p=0.001, respectively). However, when compared with the coagulation parameters 48 hours after treatment, only aPTT was significant (p=0.046). Table 2 shows the coagulation results before and after PCC administration. Regarding the dosages, 45% of the patients received 500 IU/20 mL PCC, 40% received 1000 IU/40 mL PCC, and 15% received 1500 IU/60 mL PCC.

Before treatment, 35% of the patients (n=7) had major bleeding in a critical body area, 20% (n=4) had moderate bleeding requiring hemodynamic support, and 25% (n=5) had mild bleeding. Of those with major bleeding, only one survived. When the emergency department outcomes of all patients were examined, after treatment, 25% (n=5) were discharged from the emergency department, 35% (n=7) were hospitalized in a clinic, and 40% (n=8) received follow-up care in the intensive care unit. Regarding hospital outcome, 50% (n=10) died. However, the relationship between treatment and hospital outcome was not statistically significant (p=0.42).

Four patients developed thromboembolic events after PCC administration. Two of these patients developed unstable angina pectoris with elevated cardiac markers after the administration of 500 IU/20 mL PCC. These two patients were discharged as outpatients after treatment. One of the other two patients developed acute ischemic stroke five days after the administration of 1000 IU/40 mL PCC, while the other patient developed pulmonary embolism 19 days after the administration of 1500 IU/60 mL PCC. Both patient's health outcome was death. Details are summarized in Table 3.

As part of the exploratory analyses, mortality-related clinical characteristics and laboratory results were compared between patients who survived and those who

Table 1. Demographic characteristics of the patients

Characteristics, n=20	Value
Age (years), mean ± SD	81.00±14.30
<65 years, n (%)	3 (15)
65-69 years, n (%)	0 (0)
70-74 years, n (%)	2 (10)
75-79 years, n (%)	2 (10)
>80 years, n (%)	13 (65)
Female gender, n (%)	13 (65)
Concomitant diseases	
Atrial fibrillation, n (%)	18 (90)
Hypertension, n (%)	15 (75)
Congestive heart failure, n (%)	9 (45)
Coronary artery disease, n (%)	8 (40)
Diabetes mellitus, n (%)	4 (20)
Chronic kidney disease, n (%)	4 (20)
Valvular heart disease, n (%)	3 (15)
Chronic obstructive pulmonary disease, n (%)	2 (10)
Cancer, n (%)	2 (10)
Presenting complaint	
Body bruises, n (%)	5 (25)
Shortness of breath, n (%)	4 (20)
Change in consciousness, n (%)	3 (15)
Urine with blood, n (%)	2 (10)
Bleeding from the anus, n (%)	2 (10)
Abdominal pain, n (%)	1 (5)
Vomiting with blood, n (%)	1 (5)
Deterioration in general condition, n (%)	1 (5)
Bloody stools, n (%)	1 (5)
Bleeding area	
Musculoskeletal system, n (%)	5 (25)
Gastrointestinal tract, n (%)	7 (35)
Urinary system, n (%)	2 (10)
Central nervous system, n (%)	2 (10)
No active bleeding (procedural indication), n (%)	4 (20)
Oral anticoagulant used	
Rivaroxaban, n (%)	13 (65)
Apixaban, n (%)	3 (15)
Edoxaban, n (%)	2 (10)
Dabigatran, n (%)	2 (10)
Reason for using anticoagulants	
Atrial fibrillation, n (%)	15 (75)
Valvular heart disease, n (%)	3 (15)
Pulmonary embolism, n (%)	2 (10)
Bleeding severity	
Major bleeding, n (%)	7 (35)
Moderate bleeding, n (%)	4 (20)
Mild bleeding, n (%)	5 (25)
No active bleeding, n (%)	4 (20)

Table 1. Continued

Characteristics, n=20	Value
Conditions that may pose a risk of bleeding	
Renal dysfunction, n (%)	8 (40)
Non-steroidal anti-inflammatory drug use, n (%)	4 (20)
Aspirin use, n (%)	3 (15)
SSRI use, n (%)	2 (10)
Steroid use, n (%)	1 (5)
Clopidogrel use, n (%)	1 (5)
Outcome in the emergency department	
Hospitalization in the intensive care unit, n (%)	8 (40)
Hospitalization, n (%)	7 (35)
Discharge from the emergency department, n (%)	5 (25)
Outcome after hospitalization	
Hospital discharge, n (%)	10 (50)
Death in hospital, n (%)	10 (50)
Length of hospitalization (days), median (IQR)	2.00 (0.75-7.50)

SD: Standard deviation, IQR: Interquartile range (25p, 75p), SSRI: Selective serotonin reuptake inhibitor

did not. The findings are summarized in Table 4. Patients in the mortality group more frequently presented with major bleeding compared with the non-mortality group (p=0.036). However, there were no statistically significant differences between groups regarding age, sex, DOAC type, baseline coagulation parameters (PT, aPTT, INR), or oral anticoagulant agent used. These subgroup comparisons were exploratory and interpreted with caution due to the small sample size.

Discussion

In line with international guideline recommendations, the present study found that four-factor PCC was effective in reversing the effects of DOACs and maintaining hemostasis. However, the relationship between the mortality rates of the patients and the treatment protocol applied was not found to be significant. These findings are similar to those of previous studies (11,12).

Although the use of specific antidotes, such as andexanet alfa or idarucizumab, is a priority in patients who experience major bleeding after DOAC use, it may not always be possible to obtain specific antidotes. In such cases, the use of PCC, a non-specific hemostatic agent, is recommended (10). This study investigated cases in which four-factor PCC was used because specific antidotes were not available. Improvement in coagulation parameters was detected at 4.65 hours, which is the median improvement value after treatment. This improvement period in coagulation parameters is especially important in the management of patients presenting with major life-threatening bleeding and in cases where urgent interventional procedures are planned. Additionally, in accordance with the predefined primary endpoint, PCC administration resulted in a statistically significant improvement in coagulation parameters shortly after treatment. This finding supports existing evidence indicating that PCC can provide rapid reversal of DOAC-related coagulopathy, particularly in settings where specific antidotes are not available.

Hemoglobin is the main tool used to evaluate the severity of bleeding due to DOAC use. However, standard coagulation tests (thrombin time, PT, aPTT) should be evaluated to determine the degree to which the drug contributes to bleeding in emergency conditions and the need for intervention (10). In this study, the improvements in the coagulation parameters before and right after treatment and in the coagulation parameters measured 48 hours after treatment were statistically significant. However, the INR used for warfarin was not statistically significant 48

Table 2. Statistics of laboratory parameters

Laboratory parameters	Pre-treatment	Post-treatment	p-value*	Pre-treatment	48th hour	p-value*	Post-treatment	48th hour	p-value*
PT (sec.), median (IQR)	91.20 (44.70-120.00)	32.00 (23.60-62.00	**0.001**	91.20 (44.70-120.00)	21.10 (9.80-37.10)	**0.001**	32.00 (23.60-62.00)	21.10 (9.80-37.10)	0.121
aPTT (sec.), median (IQR)	54.70 (44.40-76.00)	42.60 (34.00-56.10)	**0.003**	54.70 (44.40-76.00)	32.90 (19.60-51.70)	**0.001**	42.60 (34.00-56.10)	32.90 (19.60-51.70)	**0.046**
INR, median (IQR)	7.28 (3.67-10.60)	2.73 (1.94-4.96)	**0.001**	7.28 (3.67-10.60)	1.61 (0.78-3.00)	**0.001**	2.73 (1.94-4.96)	1.61 (0.78-3.00)	0.142

*: Wilcoxon test, IQR: Interquartile range (25p, 75p), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

Table 3. Characteristics of thromboembolic events

Type of event	Timing after PCC	PCC dose	DOAC used	Outcome
Unstable angina	<24 hours	500 IU	Rivaroxaban	Survived
Unstable angina	<24 hours	500 IU	Apixaban	Survived
Ischemic stroke	Day 5	1000 IU	Rivaroxaban	Death
Pulmonary embolism	Day 19	1500 IU	Dabigatran	Death

PCC: Prothrombin complex concentrate, DOAC: Direct oral anticoagulant, IU: International unit

Table 4. Statistical analysis between mortality and non-mortality groups

Characteristics, n=20	Mortality groups, n=10	Non-mortality groups, n=10	p-value
Age (years), mean ± SD	85.1±8.03	76.8±18.2	0.203*
Gender			
Male	4	3	0.639^
Female	6	7	
Bleeding severity			
Major bleeding	6	1	
Moderate bleeding	2	2	**0.036^**
Mild bleeding	0	5	
None	2	2	
Oral anticoagulant used			
Rivaroxaban	6	7	
Apixaban	2	1	0.220^
Edoxaban	2	0	
Dabigatran	0	2	
First presenting PT (sec.), median (IQR)	103 (IQR: 72.7-120)	49.3 (IQR: 40.1-121)	0.623#
First presenting aPTT (sec.), median (IQR)	58.1 (IQR: 47.4-63.6)	49.9 (IQR: 36.7-83.9)	0.436#
First presenting INR, median (IQR)	8.71 (IQR: 5.94-11.5)	3.98 (IQR: 3.38-10.1)	0.427#

*: Student-t test, ^: Chi-square test, #: Mann-Whitney U test, SD: Standard deviation, IQR: Interquartile range (25p, 75p), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

hours after treatment. In this study, 40% of the patients had renal dysfunction, which increased their susceptibility to bleeding. Therefore, our recommendation for future studies is that creatinine should also be measured to assess renal function and estimate the expected rate of anticoagulant drug clearance.

Bleeding is a risk with all anticoagulant therapies. However, this risk is lower with DOACs than with traditional vitamin K antagonists, such as warfarin (13). Nevertheless, caution should be exercised with respect to modifiable individual risk factors, such as hypertension, antiplatelet therapy, NSAID use, and SSRI use, which may increase susceptibility to bleeding. In this study, 75% of the patients had hypertension as a comorbidity, and 20% had a history of NSAID use, which increased their predisposition to bleeding. Meanwhile, five of the seven patients in the major bleeding group had a history of clopidogrel and/or SSRI and/or aspirin use. Patients with a history of DOAC use should be warned about drug interactions. Meanwhile, age was a non-modifiable risk factor. In this study, 65% of the patients were 80 years of age or older, and the mean age was 81.00±14.30 years, increasing the risk of bleeding. These findings underline that the clinical burden and safety concerns of PCC administration are particularly relevant to geriatric emergency medicine, where age-related vulnerability and polypharmacy are common.

To manage bleeding, it is important to determine the severity and extent of the bleeding. A patient's current clinical status guides the initial evaluation. In this study, 25% of the patients presented to the emergency department with bruising and complaints of GI tract bleeding. This rate is similar to the rates reported in previous studies (14,15). Regarding the severity of the bleeding, major bleeding ranked first, affecting 35% of the patients, and only one of these patients was discharged from the hospital. The mortality rate for all patients included in the study was 50%, which is higher than in another study (16). The relationship between health outcome and the treatment protocols applied was not significant. This high mortality rate may be attributed to the advanced age and comorbidities of the study population, the predominance of major bleeding cases involving critical organs, and delayed presentation to the emergency department. Additionally, the limited availability of specific antidotes and the retrospective nature of data collection may have influenced treatment optimization and outcomes.

Bleeding that occurs as a complication of anticoagulant treatment may lead to thromboembolic complications (TEC) after PCC is administered and the anticoagulant treatment is discontinued (17). In this study, TEC developed in four patients, and death occurred in two of four patients who received more than one dose of PCC. However, it could not be determined whether this complication was related to the PCC dosage or the discontinuation of the anticoagulant treatment.

Additionally, exploratory subgroup comparisons did not reveal statistically significant differences between survival status and baseline laboratory parameters or DOAC type; however, patients with major bleeding were more frequently represented in the mortality group,

consistent with the known severity-outcome relationship in anticoagulated emergency populations.

While the study is limited by scale and design, it reflects a real-world treatment landscape in which DOAC-treated patients are often elderly, frail, and medically complex, and where PCC may be used in the absence of specific reversal agents. This context contributes clinically relevant insight into emergency management patterns in resource-constrained settings and may help inform future prospective studies.

Study Limitations

This study has several limitations. As a retrospective study, it was limited by the documentation and accessibility of the information in the patients' medical records. Details about a patient's medical history and notes written by attending physicians in emergency department patient files are not always easily accessible. In addition, the relationship between treatment and mortality could not be determined due to the limited patient cohort design. Furthermore, it could not be determined whether the TECs that occurred were due to the PCC administration or the discontinuation of the anticoagulant therapy. Another limitation is that thromboembolic events were captured only when clinically recognized or documented within the available hospital and follow-up records; therefore, asymptomatic or post-discharge events without medical contact may have been missed. This may result in underestimation of the true incidence of TECs. During case selection, an INR >1.5 was chosen as the inclusion threshold in accordance with the institutional PCC administration protocol; however, coagulation parameters affected by the anticoagulant, such as aPTT and PT, were not specifically evaluated for each agent. An important limitation of this study is the use of INR >1.5 as both a trigger for PCC administration and an inclusion criterion in DOAC-treated patients. INR is known to be an unreliable surrogate of DOAC activity; a normal INR does not exclude clinically relevant anti-Xa or anti-IIa effects, while modest INR prolongation may be influenced by liver dysfunction, concomitant medications, or laboratory variability rather than by the DOAC itself. Consequently, INR in this cohort should be interpreted as a pragmatic marker of global coagulopathy within our institutional protocol, rather than as a precise measure of DOAC intensity. This limitation may have introduced heterogeneity in the baseline degree of anticoagulation and restricts the extent to which the observed changes in INR can be directly equated with reversal of DOAC effect. Our findings should therefore be understood as reflecting real-world PCC use in an emergency setting guided by an INR-based protocol, rather than as a mechanistic evaluation of DOAC reversal. Moreover, information regarding the timing of the last DOAC dose, renal function (estimated glomerular filtration rate), and drug-specific subgroup analyses (rivaroxaban, apixaban, dabigatran) was incomplete, which may have influenced the assessment of pharmacokinetic variability and treatment response.

Conclusion

The present study's findings showed that four-factor PCC led to a rapid and statistically significant improvement in coagulation parameters in DOAC-treated patients, both in those presenting with major bleeding and in those requiring urgent procedural intervention. However, PCC's effect on the mortality rate was not fully determined. Meanwhile, it was found that PCC might increase the risk of thromboembolism. Although PCC is an important option when specific antidotes are unavailable, the risk of complications should be considered.

Ethics

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee of Recep Tayyip Erdoğan University before the study commenced (decision no: 2025/244, date: 02.06.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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Original Article

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Synergistic Roles of Selenium and Vitamin D in Modulating Insulin Resistance and Metabolic Health

Selenyum ve D Vitamininin İnsülin Direncini ve Metabolik Sağlığı Düzenlemedeki Sinerjik Rolleri

Zeyneb İrem YÜKSEL SALDUZ[1,2], Aclan ÖZDER[1]

[1]Bezmialem Vakıf University Faculty of Medicine, Department of Family Medicine, İstanbul, Türkiye
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Family Medicine, İstanbul, Türkiye

ABSTRACT

Objective: Selenium (Se) and vitamin D are critical micronutrients linked to metabolic health and insulin sensitivity. In our study, we aimed to investigate the relationship between Se deficiency and insulin resistance (IR) in patients who were admitted for a periodic health examination, and we also aimed to explore the synergistic role of vitamin D and Se in relation to IR.

Methods: This cross-sectional study examined the association of serum Se levels, vitamin D, and IR in 161 adult patients attending periodic health examinations at the Family Medicine Outpatient Clinics of Bezmialem Vakıf University Hospital. Serum Se levels were measured by inductively coupled plasma mass spectrometry, and vitamin D levels were measured by liquid chromatography-mass spectrometry. Statistical analyses were conducted using SPSS® software (version 22). Statistical significance was set at p≤0.05.

Results: The mean age of the patients was 39.31±13.20 years. Of the study population, 72% (n=116) were female. The mean body mass index was 25.83±4.81. The mean Se level of the patients was 71.66±11.56 µg/L. Thirty-five percent of the participants had IR [homeostatic model assessment of IR (HOMA-IR ≥2.5)], with significantly higher prevalence among those with Se deficiency (<63 µg/L, p=0.016). Patients with Se deficiency had lower vitamin D levels (p=0.001) and higher HOMA-IR values (p=0.006).

Conclusion: The findings suggest a synergistic association between Se and vitamin D deficiencies and impaired insulin

ÖZ

Amaç: Selenyum (Se) ve D vitamini, metabolik sağlık ve insülin duyarlılığı ile ilişkili önemli mikro besin öğeleridir. Bu çalışmada, periyodik sağlık muayenesi için başvuran hastalarda Se eksikliği ile insülin direnci (IR) arasındaki ilişkinin araştırılması ve ayrıca D vitamini ile Se'nin IR üzerindeki olası sinerjik rolünün incelenmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışma, Bezmialem Vakıf Üniversitesi Hastanesi Aile Hekimliği polikliniklerinde periyodik sağlık muayenesine başvuran 161 yetişkin hastada serum Se düzeyleri, D vitamini ve IR arasındaki ilişkiyi incelemiştir. Serum Se düzeyleri indüktif eşleşmiş plazma kütle spektrometrisi yöntemiyle, D vitamini düzeyleri ise sıvı kromatografi-kütle spektrometrisi yöntemiyle ölçülmüştür. İstatistiksel analizler SPSS® yazılımı (versiyon 22) kullanılarak yapılmıştır. İstatistiksel anlamlılık düzeyi p≤0,05 olarak kabul edilmiştir.

Bulgular: Hastaların ortalama yaşı 39,31±13,20 yıl idi. Çalışma popülasyonunun %72'si (n=116) kadındı. Ortalama vücut kitle indeksi 25,83±4,81 olarak bulundu. Hastaların ortalama Se düzeyi 71,66±11,56 µg/L idi. Katılımcıların %35'inde IR [IR'nin homeostatik model değerlendirmesi (HOMA-IR ≥2,5)] saptandı ve Se eksikliği olanlarda IR prevalansı anlamlı olarak daha yüksekti (<63 µg/L, p=0,016). Se eksikliği olan hastalarda D vitamini düzeyleri daha düşük (p=0,001) ve HOMA-IR değerleri daha yüksek bulundu (p=0,006).

Sonuç: Bulgular, Se ve D vitamini eksiklikleri ile bozulmuş insülin duyarlılığı ve değişmiş metabolik belirteçler arasında sinerjik bir ilişki olduğunu göstermektedir. Bu çalışma, insülin

Address for Correspondence: Assoc. Prof. Zeyneb İrem Yüksel Salduz, Bezmialem Vakıf University Faculty of Medicine; İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Family Medicine, İstanbul, Türkiye
E-mail: iremsalduz@hotmail.com
ORCID IDs of the authors: Z.İ.Y.S.: 0000-0001-7730-1029, A.Ö.: 0000-0003-2254-1812

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ABSTRACT

sensitivity and altered metabolic markers. This study highlights the potential importance of Se and vitamin D in relation to IR and metabolic health. Our results indicate that addressing deficiencies in these micronutrients may be relevant for insulin sensitivity and metabolic health.

Keywords: Insulin resistance, selenium, type 2 diabetes, vitamin D

ÖZ

direnci ve metabolik sağlıkla ilişkili olarak Se ve D vitamininin potansiyel önemini vurgulamaktadır. Sonuçlarımız, bu mikro besin maddelerindeki eksikliklerin giderilmesinin insülin duyarlılığı ve metabolik sağlık açısından önemli olabileceğini göstermektedir.

Anahtar Kelimeler: İnsülin direnci, selenyum, tip 2 diyabet, vitamin D

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, affecting approximately 10% of the global population. Type 2 DM accounts for nearly 90% of all cases and is closely associated with insulin resistance (IR), a key pathophysiological mechanism in its development. IR is commonly defined by a homeostatic model assessment of IR (HOMA-IR) index above 2.5, reflecting impaired insulin sensitivity. This metabolic disturbance is linked to early alterations in glucose homeostasis, as prediabetes—defined by glycated hemoglobin (HbA1c) levels between 5.7% and 6.4%—represents an intermediate stage in which IR plays a central role and increases the risk of progression to type 2 DM. Therefore, addressing IR may be important for the prevention of prediabetes, diabetes, and related complications. Recent evidence suggests that several micronutrients are involved in glucose metabolism and may contribute to its regulation, highlighting their potential relevance in IR and prediabetic states (1-7).

Selenium (Se) and vitamin D are micronutrients implicated in metabolic health and IR. Se contributes to antioxidant defense through selenoproteins such as glutathione peroxidase (GPx) and selenoprotein S (SEPS), which support β-cell function and insulin secretion under metabolic stress. However, excessive Se exposure may adversely affect glucose metabolism, indicating a complex and dose-dependent role (8-11). Vitamin D, through its receptor expressed in β-cells and insulin-sensitive tissues, may enhance insulin secretion and sensitivity while reducing inflammation. Conversely, vitamin D deficiency has been associated with IR and impaired β-cell function (12-14).

Emerging evidence suggests potential synergistic effects of Se and vitamin D on glucose metabolism through complementary antioxidant and anti-inflammatory pathways (15,16). However, findings remain inconsistent, and studies evaluating both micronutrients in relation to IR are limited. In particular, data from Türkiye are scarce.

The present study aims to investigate the association between Se, vitamin D levels and IR in individuals undergoing routine health examinations and to evaluate the potential combined effects of vitamin D and Se. By addressing this gap, this study may contribute to a better understanding of the role of these micronutrients in metabolic health and support more comprehensive approaches to IR management.

Methods

Study Design

This research was designed as a retrospective cross-sectional study conducted in the Family Medicine Department of Bezmialem Vakıf University. The study included patients who presented for periodic health examinations between January 2023 and May 2024. Sample size calculation was performed using the website Statulator. Power was set at 0.80 and Type I error (alpha) at 0.05. Based on a mean Se level of 48 µg/L in the first group, 92 µg/L in the second group, with a standard deviation (SD) of 42 µg/L and a sampling ratio of 1, a minimum of 15 participants per group was considered sufficient (15).

Participants were classified according to Se, HOMA-IR, HbA1c and vitamin D status. For Se, patients with serum levels <63 µg/L were classified as the Se-deficient group, while those with levels ≥63 µg/L were considered Se-normal according to laboratory reference values. In addition, based on the median Se concentration observed in our study (70.63 µg/L), participants were further categorized as Se Group 1 (Se <70.63 µg/L) and Se Group 2 (Se ≥70.63 µg/L), consistent with previous reports linking lower Se levels to adverse metabolic outcomes (1,9,15). IR status was determined using the HOMA-IR index, with a cut-off of ≥2.5 defining the IR group and <2.5 the non-IR group, in line with established criteria (5). Participants without a diagnosis of diabetes were further categorized as prediabetic if their HbA1c levels were between ≥5.7% and <6.5%, and as non-prediabetic if HbA1c was <5.7%. This classification was based on the diagnostic thresholds recommended by the American Diabetes Association (ADA) (7). Vitamin D deficiency was defined as serum 25 (OH) D <20 µg/L, whereas levels ≥20 µg/L were considered sufficient, based on widely accepted guidelines (14,16).

Patient Selection (Inclusion and Exclusion Criteria)

A total of 161 patients aged 18-65 years, of both genders, who presented for periodic health examinations were included. Exclusion criteria were: history of diabetes, hypertension, hyperlipidemia, thyroid or parathyroid

disorders, chronic liver disease, chronic kidney failure, febrile illnesses, pregnancy, and the use of medications or supplements that could affect Se levels (including Se or multivitamin supplementation). Participants with abnormal laboratory results were also excluded. Type 2 DM was diagnosed if the fasting plasma glucose was higher than 126 mg/dL, 2-h post-challenged plasma glucose was above 200 mg/dL, or HbA1c ≥6.5%. This was based on the recommendation of ADA (7).

Data Collection

Data were collected using a routine structured form, which included demographic information [age, sex, body mass index (BMI), smoking status], medical history (chronic diseases, medication use), and lifestyle characteristics. Anthropometric measurements (weight, height) were recorded. These data were obtained from outpatient follow-up records. BMI (kg/m²) was calculated as weight in kilograms divided by the square of height in meters, according to the World Health Organization definition (17). IR was calculated using HOMA-IR formula: fasting insulin (μU/mL)×fasting glucose (mg/dL)/405, as originally described by Matthews et al. (5).

Laboratory Measurements

Subjects were requested to visit the family medicine outpatient clinic for blood withdrawal after fasting overnight for ≥8 hours. At the screening visit, blood samples were collected for blood tests [among the laboratory data were Se, vitamin D, HOMA-IR, HbA1c, fasting blood glucose (FBG), urea, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), uric acid, albumin, protein total, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), calcium (Ca), sodium (Na), potassium (K), chloride (Cl), iron (Fe), ferritin, thyroid-stimulating hormone (TSH), C-reactive protein (CRP), sedimentation, white blood cell (WBC), red blood cell (RBC), platelet (PLT), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR)]. Venous blood samples taken after fasting were collected in a dipotassium ethylenediaminetetraacetic acid tube for complete blood counts (CBC) testing and in a vacuum tube for biochemical tests. Samples were transported at room temperature and analyzed within 1 h to minimize changes due to standing. After the vacuum tube was centrifuged at 2500×g for 10 minutes, the parameters included in the study were analyzed in the Medical Biochemistry Laboratory of Bezmialem University Hospital. Se was measured by inductively coupled plasma mass spectrometry (Acıbadem LabMED). Serum 25 (OH) D was measured by liquid chromatography-mass spectrometry method (Zivak 25 (OH) D2-D3 kit, Tandem Gold 325-MS model, USA). Levels of HbA1c (%) were measured quantitatively using immunoturbidimetry from whole blood (Archem Diagnostics HbA1c kit, Siemens Atellica® CH 930 analyzer). The glucose oxidase method was used to analyse plasma glucose levels (Siemens Atellica® CH 930 analyzer, Germany). Lipid profile and other biochemical parameters were measured using a chemical auto-analyzer (Siemens Atellica® CH 930 analyzer, Germany). Parameters of CBC were measured using an automated haematology analyser (Sysmex XN1000, Germany).

Ethical Considerations

The study received approval from the Bezmialem Vakıf University Clinical Research Ethics Committee (approval no: 2024/194, dated 31.05.2024). The study was registered under ClinicalTrials registration number: E-54022451-050.04-152508.

Statistical Analysis

Data were analyzed using SPSS® software for Window® version 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics for qualitative variables were presented as frequency (n) and percentage (%), while quantitative variables were summarized using mean, median, SD, minimum, and maximum values. The normality of quantitative variables was assessed using the Shapiro-Wilk test, and the Levene's test was employed to evaluate the homogeneity of variance. The differences between groups were compared using Student's t-test, chi-square tests, Spearman's correlation test, binary logistic regression and two steps cluster analysis. Data were expressed as mean and SD. The statistical significance was set at the p-value of ≤0.05.

Results

The mean age of the patients was 39.31±13.20 years. Of the patients 72% (n=116) were women. The mean of BMI was 25.83±4.81. The HOMA-IR value of the patients was above 2.5 in 57 patients. Forty-five patients had low Se levels (serum Se <63 μg/L). Among the laboratory data, urea, BUN, creatinine, eGFR, albumin, LDL-C, Ca, HCT, HGB were statistically significant between the groups. However, vitamin D and HOMA-IR values were statistically and clinically significantly different between the groups (p≤0.05) (Table 1).

Levels of Se was low in 40% of patients with IR. Levels of Se was low in 21% of patients with non-IR. The differences were significant (p=0.016) (Table 2).

Based on available HbA1c data after excluding missing values, the study population consisted of 141 participants. In Se group 1, mean age was found to be significantly lower than the mean age of group 2 (p=0.043). In Se group 1, mean vitamin D level was found to be significantly lower than mean vitamin D level of group 2 (p<0.001). In Se group 1 (Se median <70.63), mean urea level was found to be significantly lower than the mean urea level of group 2 (Se median ≥70.63) (p<0.001). In Se group 1, mean BUN level was found to be significantly lower than the mean BUN

Table 1. The comparison of results between patients Se-deficient and normal

	Se-deficient (Se <63 µg/L) n=45	Se-normal (Se ≥63 µg/L) n=116	p-value
Vitamin D (µg/L)	14.31±8.34	20.33±11.36	**0.001**
HOMA-IR	3.09±1.91	2.33±1.33	**0.006**
Urea (mg/dL)	23.46±5.88	27.64±5.73	**0.001**
BUN (mg/dL)	10.32±2.61	12.64±2.95	**0.001**
Creatinine (mg/dL)	0.72±0.15	0.78±0.16	**0.028**
eGFR (mL/min/1.73 m²)	108.21±13.73	100.72±18.55	**0.014**
Albumin (g/dL)	4.68±0.37	4.71±0.24	**0.001**
LDL-C (mg/dL)	110.32±35.54	123.65±35.23	**0.047**
Ca (mg/dL)	9.54±0.31	9.76±0.48	**0.042**
HCT (%)	39.93±3.32	41.38±3.92	**0.043**
HGB (g/dL)	13.24±1.41	13.62±1.68	**0.038**

Note 1: Vitamin D (20-70 µg/L) HOMA-IR (<2.5) urea (12.8-42.8 mg/dL) BUN (6-20 mg/dL) creatinine (0.6-1.3 mg/dL) eGFR (>90 mL/min/1.73 m²) albumin (3.5-5 g/dL) LDL-C (<100 mg/dL) Ca (8.3-10.6 mg/dL) HCT (male 40-52%, female 35.5-48%) HGB (male 14.1-17.5 g/dL, female 12.2-16.2 g/dL)
Note 2: Data are presented as mean ± standard deviation (SD)
HOMA-IR: Homeostasis model assessment of insulin resistance, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein cholesterol, Ca: Calcium, HCT: Hematocrit, HGB: Hemoglobin, Se: Selenium

Table 2. The comparison of Se levels between IR and non-IR groups

	IR group (HOMA-IR ≥2.5) n=57	Non-IR group (HOMA-IR <2.5) n=104	p-value
Se-deficient (Se <63 µg/L) n=45	23/57 (40%)	22/104 (21%)	**0.016**
Se-normal (Se ≥63 µg/L) n=116	34/57 (60%)	82/104 (79%)	

Note: Data are presented as percentages (%)
HOMA-IR: Homeostasis model assessment of insulin resistance, Se: Selenium

level of group 2 (p<0.001). In Se group 1, mean creatinine level was found to be significantly lower than the mean creatinine level of group 2 (p=0.006). In Se group 1, mean eGFR was found to be significantly higher than the mean eGFR of group 2 (p=0.002). In Se group 1, mean albumin level was found to be significantly lower than the mean albumin level of group 2 (p<0.001). In Se group 1, mean total protein level was found to be significantly lower than the mean total protein level of group (p=0.009). In Se group 1, mean LDL-C level was found to be significantly lower than the mean LDL-C level of group 2 (p=0.03). In Se group 1, mean Ca level was found to be significantly lower than the mean Ca level of group 2 (p=0.013). In Se group 1, mean ferritin level was found to be significantly lower than mean ferritin level of group 2 (p=0.013). Other significant differences are presented in Table 3.

When we evaluated Se levels according to median level which was 70.63 µg/L; prediabetic patients group had significantly lower Se level (p=0.026) (Table 4).

In the results of binary logistic regression analysis (chi-square value was 6.361, p-value was 0.607, the Nagelkerke R-square value: 0.570). Albumin level was found to have a strong relationship with Se level. Those with high albumin levels were more likely to have high Se levels (p=0.022, odds ratio: 64.728). Total protein level, which was very close to the significance limit, stood out as another variable that might affect Se levels (p=0.073). Other variables were not found to be statistically significant (p>0.05).

Additionally, cluster analysis was performed. The most influential variables in grouping patients with similar clinical characteristics into clusters were determined to be HCT, HGB, creatinine, RBC, age, ferritin, eGFR, BUN urea, and HbA1c (Figure 1).

A significant difference in Se levels was observed between the clusters obtained from the clustering analysis (p=0.023). As a conclusion of cluster analysis, individuals with low Se levels also tended to have significantly lower mean values in age, BUN, urea, creatinine, LDL-C, RBC, HGB, HCT, and ferritin levels (p<0.001). This pattern suggests a possible association between low Se status and reduced levels in these physiological and biochemical markers, which may reflect a shared underlying factor or biological mechanism influencing both Se and these variables.

Discussion

In this single-center outpatient sample of adult patients, we observed significant differences in serum Se, vitamin D, HOMA-IR, and HbA1c levels between the groups. Vitamin D levels were significantly lower, while HOMA-IR values were significantly higher, in the low serum Se group. The current study extends previous findings on the association between serum Se level, vitamin D level and IR.

International evidence suggests that serum Se concentrations in healthy populations are generally around or below the 80 µg/L threshold, and many populations do not consistently reach this level (18-20). In contrast, Karataş et al. reported a higher mean Se level of 85.81±10.84 µg/L in a control group of Turkish adults, although the overall mean in their study was lower (76.49±11.36 µg/L) (21). In our cohort, the mean serum Se level was 71.66±11.56 µg/L, representing one of the lowest values among the referenced studies. These differences may reflect regional variability in Se status, potentially related to soil composition, dietary patterns, and environmental availability.

The role of Se in the management of IR remains a subject of ongoing debate. Our findings are consistent with

Table 3. The comparison of results between selenium (Se) groups 1 and 2

	Se group 1 (Se median<70.63 µg/L) n=71	**Se group 2 (Se median ≥70.63 µg/L) n=70**	**p-value**
Age	36.60±13.04 34 (26-46)	40.29±12.58 41 (30-50)	**0.043**
BMI (kg/m²)	26.58±5.76 24.97 (22.7-30.66)	25.09±4.02 25.21 (22.85-27.24)	0.349
Vitamin D (µg/L)	15.87±8.47 14.34 (8.81-20.97)	21.67±12.61 18.60 (14.78-25.20)	**0.001**
HOMA-IR	2.58±1.72 1.87 (1.37-3.27)	2.24±1.12 2.08 (1.46-2.69)	0.734
HbA1c (%)	5.25±0.37 5.19 (5.03-5.49)	5.16±0.36 5.10 (4.88-5.42)	0.120
FBG (mg/dL)	92.49±10.82	91.31±8.81	0.463
Urea (mg/dL)	23.46±5.88 24 (19-28)	27.64±5.73 28 (24-30.50)	**0.001**
BUN (mg/dL)	10.96±2.74	12.88±2.66	**0.001**
Creatinine (mg/dL)	0.73±0.13 0.70 (0.64-0.79)	0.80±0.15 0.78 (0.68-0.89)	**0.006**
eGFR (mL/min/1.73 m²)	107.36±16.43 109 (96-120)	98.76±18.03 101 (92-109)	**0.002**
Uric acid (mg/dL)	4.58±1.29 4.4 (3.80-5.3)	4.88±1.35 4.85 (4-5.50)	0.163
Albumin (g/dL)	4.61±0.24 4.7 (4.50-4.80)	4.78±0.19 4.8 (4.70-4.90)	**0.001**
Protein total (g/dL)	7.33±0.37 7.30 (7.10-7.60)	7.48±0.32 7.45 (7.30-7.62)	**0.009**
TG (mg/dL)	108.75±62.23 90 (67-133)	112.96±57.99 98 (69.5-138)	0.347
HDL-C (mg/dL)	56.12±14.59 53.15 (47.05-66.52)	58.5±15.50 56.05 (49.07-67.77)	0.263
LDL-C (mg/dL)	109.93±35.86	127.10±33.81	**0.003**
ALT (U/L)	20.25±15.16 16 (13-23)	27.49±25.12 19.5 (13-30.25)	0.058
Ca (mg/dL)	9.60±0.31 9.60 (9.30-9.80)	9.74±0.38 9.80 (9.50-10)	**0.013**
Na (mmol/L)	139.14±1.93 139 (138-141)	139.44±1.88 139 (138-141)	0.522
K (mmol/L)	5.73±1.81 4.33 (4.15-5.75)	4.31±0.28 4.34 (4.15-4.50)	0.462
Cl (mmol/L)	104.73±2.47 104 (103.75-106.25)	104.12±2.20 104 (102-106)	0.114
Fe (µg/dL)	84.24±42.23 82 (53-112)	95.22±40.79 85 (69-124.75)	0.120
Ferritin (µg/L)	33.60±54.09 15.51 (6.48-42.01)	40.77±42.47 29.20 (12.21-50.47)	**0.013**
TSH (mIU/L)	2.43±1.91 2 (1.16-3)	2.38±1.43 2.02 (1.51-2.96)	0.703

Table 3. Continued

	Se group 1 (Se median<70.63 µg/L) n=71	Se group 2 (Se median ≥70.63 µg/L) n=70	p-value
CRP (mg/L)	2.07±2.80 0.96 (0.26-2.67)	2.15±3.77 0.54 (0.20-2.14)	0.187
Sedimentation (mm/h)	9.63±6.50 7 (4-14)	7.40±4.38 6 (4-10)	0.069

Note 1: BMI (18.5-24.9 kg/m²) vitamin D (20-70 µg/L) HOMA-IR (<2.5) HbA1c (<6.5%) FBG (70-105 mg/dL) urea (12.8-42.8 mg/dL) BUN (6-20 mg/dL) creatinine (0.6-1.3 mg/dL) eGFR (>90 mL/min/1.73 m²) uric acid (3.1-7.8 mg/dL) albumin (3.5-5 g/dL) protein total (5.7-8.2 g/dL) TG (<150 mg/dL) HDL-C (>40 mg/dL) LDL-C (<100 mg/dL) ALT (10-49 U/L) Ca (8.3-10.6 mg/dL) Na (135-145 mmol/L) K (3.5-5.1 mmol/L) Cl (98-107 mmol/L) Fe (50-170 µg/dL) Ferritin (22-322 µg/L) TSH (0.55-4.78 mIU/L) CRP (0-5 mg/L) sedimentation (0-20 mm/h)
Note 2: In the tables, normally distributed quantitative variables are presented as mean ± standard deviation, whereas non-normally distributed variables are presented as median (minimum-maximum) values
BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance, HbA1c: Glycated hemoglobin, FBG: Fasting blood glucose, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, ALT: Aminotransferase, Ca: Calcium, Na: Sodium, K: Potassium, Cl: Chloride, Fe: Iron, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein

Table 4. The comparison of HbA1c levels between selenium (Se) groups 1 and 2

	Selenium group 1 (Se median <70.63 µg/L) n=71	Selenium group 2 (Se median ≥70.63 µg/L) n=70	p-value
Prediabetic (HbA1c ≥5.7-<6.5) n=14	11/71 (15%)	3/70 (4%)	**0.026**
Non-prediabetic (HbA1c <5.7) n=127	60/71 (85%)	67/70 (96%)	

Note: Data are presented as percentages (%), HbA1c: Glycated hemoglobin

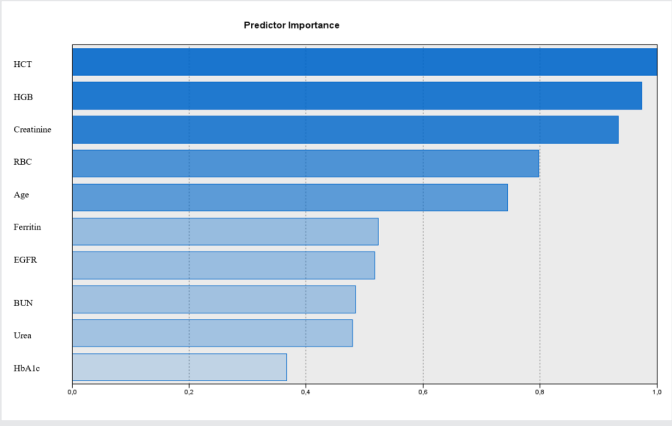

Figure 1. This figure shows the parameters selected for cluster analysis, including HCT, HGB, creatinine, RBC, age, ferritin, eGFR, BUN, urea, and HbA1c levels. These variables were chosen to explore potential associations among physiological and biochemical markers within the identified clusters

HCT: Hematocrit, HGB: Hemoglobin, RBC: Red blood cell, eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, HbA1c: Glycated hemoglobin

previous studies, showing higher HOMA-IR and HbA1c levels in participants with lower serum Se concentrations (22-24). This observation supports the hypothesis that Se deficiency may be associated with poorer glycemic control. However, while observational evidence suggests an inverse association between Se levels and diabetes prevalence, causality remains uncertain. Further randomized controlled trials are needed to clarify whether Se supplementation may have a role in the prevention or management of diabetes. In addition, variability in baseline Se levels across populations underscores the need to further investigate potential regional and genetic factors influencing Se metabolism and its effects on glucose regulation.

A plausible biological mechanism underlying the inverse association between serum Se levels and IR may involve its effect on GPx activity. GPx contributes to cellular redox balance by reducing hydrogen peroxide (H_2O_2), and lower intracellular H_2O_2 levels may be associated with reduced activity of protein tyrosine phosphatase 1B (PTP1B). This, in turn, may support insulin receptor signaling and improve insulin sensitivity (25-27). However, findings in the literature are inconsistent. Some studies have reported positive associations between higher serum Se levels and increased risk of elevated fasting glucose or prediabetes (28-32). One possible explanation is the link between Se and obesity-related processes, including adipose tissue expansion, chronic inflammation, and oxidative stress (33). Through selenoproteins such as GPx, selenoprotein P (SEPP), and others, Se may influence insulin signaling in hepatic and muscle tissues (34). In particular, elevated Se and SEPP levels have been associated with prediabetes markers, potentially through effects on insulin signaling pathways, including altered phosphorylation of protein kinase B and partial inhibition of AMP-activated protein kinase (35,36). Nevertheless, other studies have found no significant association between serum Se levels and glucose metabolism or IR (37,38).

The relationship between Se and prediabetes in both animal and human studies remains ambiguous, primarily due to conflicting findings reported in the literature. Some studies have indicated positive associations, while others have observed negative associations or no

significant relationships. This inconsistency may stem from several factors, including a potential U-shaped relationship between Se levels and prediabetes, variations in epidemiological research methodologies, differences in sample sizes, the use of diverse biomarkers for Se, and the presence of single nucleotide polymorphisms in genes encoding selenoproteins.

Studies have shown that vitamin D deficiency is associated with an increased risk of IR and prediabetes. Most studies examining minerals and trace elements in relation to IR and diabetes have focused on these components independently (14,16). However, the present study evaluates vitamin D and Se deficiencies concurrently, which may provide insight into their combined roles and potential interactions in metabolic health and IR.

The synergistic roles of Se and vitamin D in relation to IR and metabolic health may be related to their complementary mechanisms. Se's antioxidant properties may help protect pancreatic β-cells and support redox balance, which may be associated with reduced oxidative stress-related IR (9). Vitamin D, through its receptor in β-cells and glucose-metabolizing tissues, may contribute to insulin secretion and sensitivity by modulating Ca signaling and inflammatory pathways (14). Combined, optimal levels of these micronutrients may support metabolic pathways, reducing IR risk and associated conditions. Further research into their combined supplementation is warranted.

Study Limitations

This study has several limitations. First, its single-center, retrospective, cross-sectional design did not allow for the determination of causal relationships between Se concentrations and IR. Furthermore, crucial data on dietary habits, living environment, ethnicity, and medication use (including vitamins, trace element supplements, and diuretics) were not collected, which may have affected the findings. In particular, the absence of data on dietary intake and sunlight exposure—both of which can significantly influence vitamin D levels—may have confounded the observed associations. Additionally, selenoproteins, which are critical indicators of Se function in the human body, were not measured. Using only HOMA-IR to assess IR was also limiting. A limitation of this study was the incomplete availability of HbA1c data. Although HOMA-IR was measured in all participants, HbA1c testing was performed only when clinically indicated during routine follow-up for glycemic control, resulting in available data for 141 individuals. This selective measurement might introduce selection bias and limit the generalizability of HbA1c-related findings. Including insulin-independent IR markers would strengthen the study, and this point could be suggested for future research. Future studies should aim to measure the concentrations or activities of multiple selenoproteins to validate the observed association between Se and prediabetes.

Conclusion

In conclusion, recent findings suggest a synergistic relationship between Se and vitamin D in relation to IR. Both micronutrients are essential for metabolic health, and deficiencies in either have been associated with an increased risk of IR and type 2 DM. In our study, we observed that lower vitamin D and Se levels were associated with elevated IR, further suggesting the potential relevance of adequate levels of both vitamin D and Se in metabolic regulation. These results may indicate that addressing deficiencies in these micronutrients could be associated with improved insulin sensitivity and metabolic health.

Ethics

Ethics Committee Approval: The study received approval from the Bezmialem Vakıf University Clinical Research Ethics Committee (approval no: 2024/194, dated 31.05.2024).

Informed Consent: Retrospective study.

Acknowledgments

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Footnotes

Authorship Contributions

Concept: Z.İ.Y.S., Design: Z.İ.Y.S., Data Collection or Processing: Z.İ.Y.S., Analysis or Interpretation: Z.İ.Y.S., A.Ö., Literature Search: Z.İ.Y.S., Writing: Z.İ.Y.S.

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

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Original Article

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Nevus Sebaceus of Jadassohn: A Clinicopathological and Dermoscopic Study with Management Implications

Jadassohn'un Nevus Sebaseus'u: Klinikopatolojik ve Dermoskopik Bulgular ile Tedaviye Yönelik Çıkarımlar

Gökhan KAYA[1], Melin ÖZGÜN GEÇER[2], Ceren ALAVANDA[3], Ayşegül YABACI TAK[4]

[1]Sivas Medicana Hospital, Clinic of Dermatology, Sivas, Türkiye
[2]Yeditepe University Koşuyolu Hospital, Clinic of Pathology, İstanbul, Türkiye
[3]İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics, İstanbul, Türkiye
[4]Bezmialem Vakıf University Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Türkiye

ABSTRACT

Objective: Nevus sebaceus (NS) of Jadassohn is a congenital hamartoma that undergoes stage-dependent morphological changes. Although malignant transformation is rare, long-term monitoring is advised. To describe the clinical, dermoscopic, and histopathological features of NS and to assess dermoscopy-histopathology correlations.

Methods: Twenty-five patients were retrospectively analyzed over 2.5 years. All patients underwent clinical staging and dermoscopy. Biopsy procedures were performed in 15 patients, and complete histopathological data suitable for analysis were available for 13 (52.0%) patients. Fisher's exact and Spearman's correlation tests were used.

Results: Mean age was 17.9±11.9 years (range: 3-43); 56.0% were male. Lesions were mainly on the scalp (60.0%). Clinical staging identified infantile (28.0%), early proliferative (24.0%), verrucous (32.0%), and nodular (16.0%) lesions. Mean age differed significantly across stages (analysis of variance, p=0.045), though overlap between groups suggested staging is not determined by age alone. Yellowish globules were significantly associated with early stages (p=0.005), whereas grayish papillary structures were confined to advanced stages (p=0.005). Arborizing vessels and brown globules were more frequent in advanced lesions but not statistically significant. Histopathology revealed basaloid epidermal proliferation, immature hair follicles, immature sebaceous glands, and

ÖZ

Amaç: Jadassohn'un nevus sebaseus'u (NS), evreye bağlı morfolojik değişiklikler gösteren konjenital bir hamartomdur. Malign transformasyon nadirdir ancak uzun dönem takip önerilmektedir. Bu çalışmanın amacı, NS'nin klinik, dermoskopik ve histopatolojik özelliklerini tanımlamak ve dermoskopi-histopatoloji korelasyonlarını değerlendirmektir.

Yöntemler: NS tanılı 25 hasta 2,5 yıllık bir sürede retrospektif olarak incelendi. Tüm olgularda klinik evreleme ve dermoskopik değerlendirme yapıldı. On beş hastada biyopsi uygulanmış olup, analiz için uygun ayrıntılı histopatolojik veri 13 hastada (%52,0) mevcuttu. Fisher's exact ve Spearman korelasyon testleri kullanıldı.

Bulgular: Ortalama yaş 17,9±11,9 yıl (dağılım: 3-43) olup, hastaların %56,0'sı erkekti. Lezyonlar en sık skalpte (%60,0) izlendi. Klinik evreler; infantil %28,0, erken proliferatif %24,0, verrüköz %32,0 ve nodüler %16,0 olarak dağıldı. Ortalama yaş evreler arasında anlamlı farklılık gösterdi (varyans analizi, p=0,045), ancak gruplar arası örtüşme evrelemenin yalnızca yaşa bağlı olmadığını düşündürdü. Sarımsı globüller erken evrelerle anlamlı ilişkiliydi (p=0,005), gri papilliform yapılar ise yalnızca ileri evrelerde görüldü (p=0,005). İnce arborizan damarlar ve kahverengi globüller ileri evrelerde daha sık olmakla birlikte anlamlı bulunmadı. Histopatolojik incelemede bazaloid epidermal proliferasyon, immatür saç folliküleri, immatür sebase bezler ve perifoliküler inflamasyon yaygın

Address for Correspondence: Gökhan Kaya MD, Sivas Medicana Hospital, Clinic of Dermatology, Sivas, Türkiye
E-mail: gkhnkya@gmail.com
ORCID IDs of the authors: G.K.: 0000-0002-9651-4115, M.Ö.G.: 0000-0003-4849-0793, C.A.: 0000-0002-7327-3849, A.Y.T.: 0000-0002-5813-3397

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ABSTRACT

perifollicular inflammation as common features. No statistically significant dermoscopy-histopathology associations were identified. No malignant transformation was observed.

Conclusion: Dermoscopy provides stage-dependent diagnostic clues in NS and complements histopathology as a non-invasive tool for evaluation and follow-up. Conservative surveillance may be appropriate in selected low-risk cases, whereas surgical excision remains recommended for advanced or clinically suspicious lesions.

Keywords: Nevus sebaceus, dermoscopy, trichoscopy, histopathology, sebaceous gland hyperplasia, adnexal tumors, trichoblastoma, basal cell carcinoma, RASopathy, cutaneous hamartoma

ÖZ

bulgulardı. Dermoskopik ve histopatolojik bulgular arasında istatistiksel olarak anlamlı bir ilişki saptanmadı. Malignite gözlenmedi.

Sonuç: Dermoskopi, NS'ta evreye bağlı tanısal ipuçları sağlar ve histopatolojiyi tamamlayıcı, non-invaziv bir değerlendirme aracı olarak öne çıkar. Düşük riskli olgularda konservatif izlem uygun olabilirken, ileri evre veya klinik olarak şüpheli lezyonlarda cerrahi eksizyon önerilmektedir.

Anahtar Kelimeler: Nevus sebaseus, dermoskopi, trikoskopi, histopatoloji, sebase bez hiperplazisi, adneksal tümör, trikoblastom, bazal hücreli karsinom, RASopati, deri hamartomu

Introduction

Nevus sebaceus (NS) of Jadassohn is a congenital cutaneous hamartoma characterized by sebaceous hyperplasia and adnexal abnormalities of the epidermis, pilosebaceous units, and sweat glands. The term organoid nevus has also been used to emphasize its multi-lineage adnexal differentiation. Clinically, NS progresses through distinct stages: in infancy, it appears as a smooth, hairless, yellowish plaque; during puberty, hormonal influences induce sebaceous hyperplasia, epidermal thickening, and a verrucous transformation (1,2).

NS may occur sporadically or with syndromic associations that include extracutaneous manifestations. Its prevalence is estimated at 0.1-0.3% in newborns, it predominantly involves the head and neck, and it is often accompanied by localized alopecia due to the absence of terminal follicles (3,4).

Histologically, infantile lesions show immature sebaceous lobules and reduced hair follicles, whereas adolescence triggers epidermal hyperplasia and adnexal enlargement. Recently, "sebaceous holes" have been proposed as a histological clue that helps distinguish NS from classic sebaceous hyperplasia (5). In adulthood, secondary tumors may develop—predominantly benign adnexal neoplasms such as syringocystadenoma papilliferum and trichoblastoma—while malignant potential appears low; basal cell carcinoma risk is generally estimated at <1% (2,6).

At the molecular level, NS is classified as a mosaic RASopathy caused by postzygotic activating mutations in Harvey rat sarcoma viral oncogene homolog or Kirsten rat sarcoma viral oncogene homolog, which result in constitutive activation of the RAS/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase-AKT pathway signaling pathways (7-9). These aberrant signaling cascades underlie the characteristic adnexal differentiation, sebaceous hyperplasia, and stage-dependent clinical evolution of the lesion. Differential diagnoses include epidermal nevus, nevoid sebaceous hyperplasia (NSH), sebaceous hyperplasia, and *aplasia cutis congenita* (ACC), and several cases have been misclassified due to overlapping clinical features (10-12). Moreover, epidermal nevus shares similar mutational profiles and clinicopathologic characteristics, placing both entities along the same spectrum of mosaic RASopathies (13). These sequential molecular and clinicopathological transitions are summarized schematically in Figure 1.

The mainstay of management remains complete excision in lesions with suspected neoplastic change; Mohs micrographic surgery is preferred in malignant transformation, while ablative and laser-based modalities may provide cosmetic benefits but carry a risk of recurrence (14). Despite multiple descriptive reports, quantitative data integrating clinical staging, dermoscopic patterns, and histopathological correlations remain limited. This study therefore aimed to investigate the clinical, dermoscopic, and histopathological features of NS in a well-defined cohort, with emphasis on stage-dependent findings and their implications for diagnosis and management (15,16).

Methods

Study Design and Study Population

This retrospective observational study was conducted at Nizip State Hospital, a public secondary care center in Gaziantep, Türkiye, over a 2.5-year period (2023-2025). Consecutive patients with a diagnosis of NS were screened; twenty-five met eligibility criteria and underwent standardized clinical and dermoscopic evaluation. Biopsy procedures were performed in 15 patients, and complete histopathological data suitable for detailed evaluation were available for 13 cases. The inclusion criterion was clinically and/or histopathologically confirmed NS with dermoscopic documentation. Exclusion criteria were incomplete records, absence of dermoscopic documentation, insufficient clinical/dermoscopic criteria for NS or histopathological findings incompatible with NS, extensive concomitant conditions likely to confound assessment (e.g., widespread epidermal nevus, congenital melanocytic nevus, inflammatory dermatoses), and

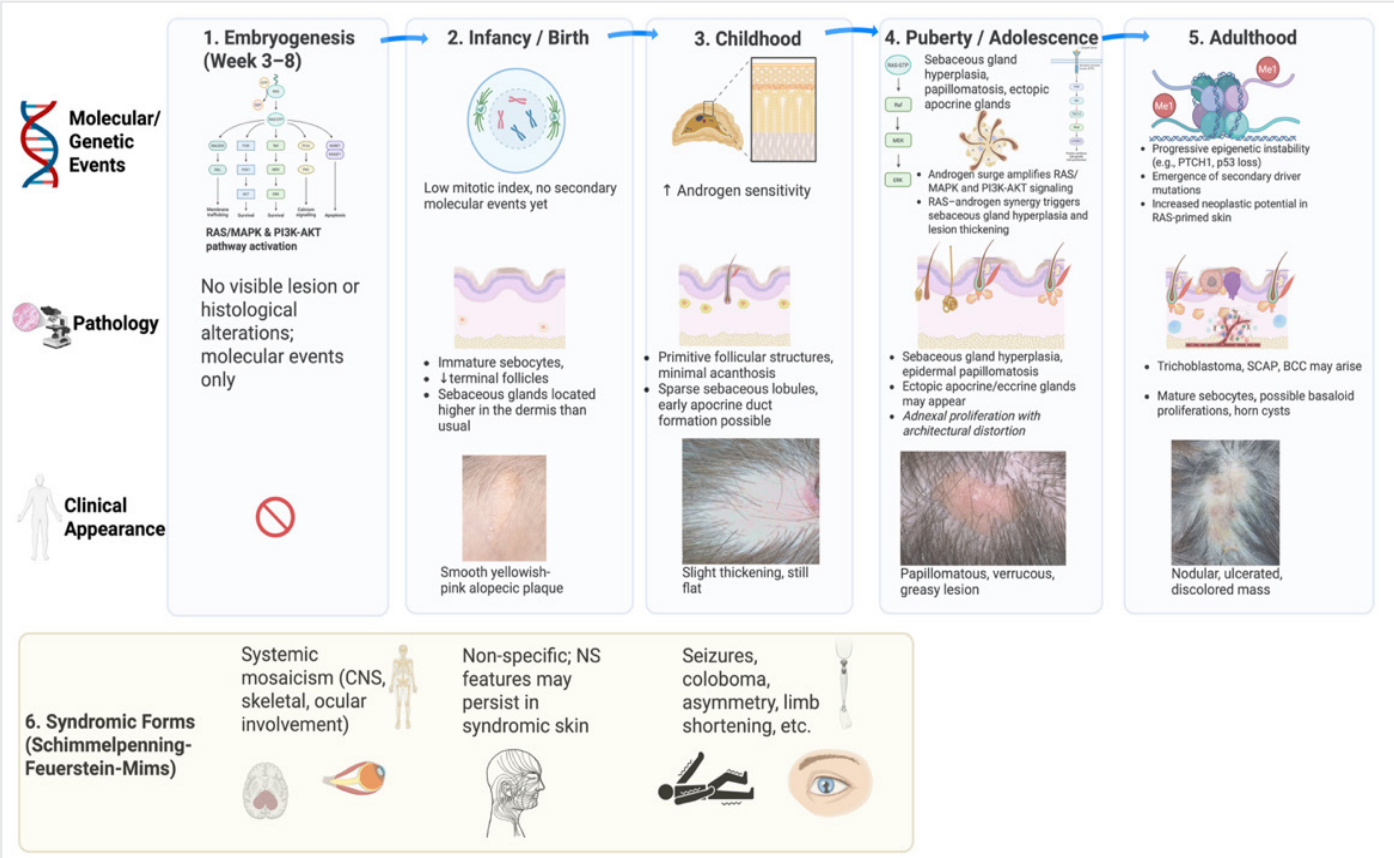

Figure 1. Timeline-based schematic representation of the molecular, histopathological, and clinical evolution of NS

Postzygotic HRAS or KRAS pathogenic variants that occur during embryogenesis initiate mosaic RASopathy, resulting in localized skin lesions. The persistent activation of the RAS/MAPK and PI3K-AKT pathways, exacerbated by pubertal androgens, drives sebaceous hyperplasia and adnexal architectural changes. Histopathologic findings progress with age, transitioning from immature sebocytes and absent terminal follicles to sebaceous proliferation, and potential neoplasia. Clinical features follow this trajectory, evolving from smooth alopecic plaques in infancy to papillomatous or nodular lesions in adulthood. Syndromic forms, such as Schimmelpenning-Feuerstein-Mims syndrome, reflect systemic mosaicism with CNS, ocular, and skeletal involvement. Additionally, NS-associated sebocytes may exhibit endocrine-like activity, secrete cytokines, and respond to neurohormonal stimuli, thereby modulating the progression of lesions and local immunity

HRAS: Harvey rat sarcoma viral oncogene homolog, KRAS: Kirsten rat sarcoma viral oncogene homolog, MAPK: Mitogen-activated protein kinase, PI3K-AKT: Phosphoinositide 3-kinase-AKT pathway, CNS: Central nervous system, NS: Nevus sebaceus, BCC: Basal cell carcinoma

suspected but unconfirmed syndromic NS. Conservatively managed patients were followed annually with clinical and dermoscopic assessment for at least one year to document stability.

Clinical and Dermoscopic Evaluation

Demographics (age, sex), lesion site, surface morphology, and associated features (alopecia, verrucous texture, pigmentation) were recorded. Clinical and dermoscopic staging followed published criteria (15,16). Briefly, the infantile stage shows clustered yellow globules on a pale-yellow or pink background with preserved follicular openings; the early proliferative plaque stage is characterized by lobulated, cobblestone-like yellow structures occasionally with perifollicular change; the verrucous stage presents a cerebriform surface with yellow-white scaling or crusting, polymorphous vascular patterns, and partial follicular obliteration; and the advanced or nodular stage exhibits nodular surface architecture, dense keratinization, complete follicular loss, and atypical vascular structures (e.g., fine arborizing or irregular vessels) that may prompt closer surveillance.

Dermoscopy was performed using a DermLite DL5 at 10× magnification (DermLite, San Juan Capistrano, CA, USA), and images were archived in secure digital repositories. Age and lesion site were recorded but not used for staging. Representative clinical and dermoscopic images across different evolutionary stages of NS are presented in Figure 2. Representative differentials excluded from the cohort, such as epidermal nevus, ACC, NSH, juvenile xanthogranuloma, and temporal triangular alopecia, are illustrated in Figure 3.

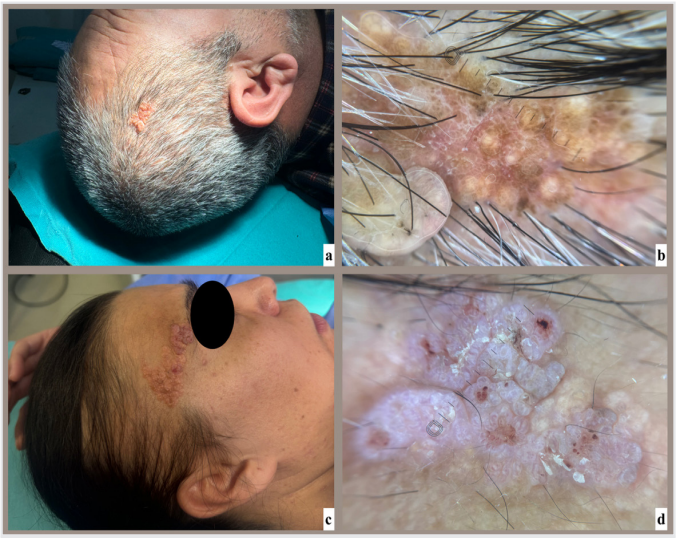

Figure 2. Clinical and dermoscopic features of nevus sebaceus (NS)

(a) Clinical image of a 43-year-old male patient presenting with a well-demarcated, yellowish verrucous plaque on the vertex scalp, showing partial alopecia and irregular surface texture. (b) Dermoscopic view of the same lesion revealing clustered yellow lobular structures, a cerebriform pattern, loss of follicular openings, and fine arborizing vessels—typical of advanced-stage NS. (c) Clinical presentation of a 34-year-old female with a brownish, verrucous plaque in the frontal region extending to the hairline, accompanied by localized alopecia. (d) Dermoscopic features of the same lesion showing whitish lobulated structures, polymorphous and fine linear vessels, along with crusted erosions—consistent with the verrucous stage of NS

Histopathological Evaluation

Biopsy specimens were fixed in 10% neutral-buffered formalin, routinely processed, paraffin-embedded, and stained with hematoxylin and eosin. Where adnexal differentiation or neoplasia was suspected, additional immunohistochemical stains were applied according to standard diagnostic practice. Microscopic assessment encompassed epidermal changes (acanthosis, papillomatosis, basal layer pigmentation), follicular structures (terminal hair development, follicular differentiation, perifollicular inflammation), and adnexal elements (presence and maturity of sebaceous glands, sebaceous hyperplasia, and eccrine or apocrine ductal proliferation). Illustrative dermoscopy-histopathology pairings are shown in Figure 4.

Ethical Approval Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethical approval was obtained from the Scientific Research Ethics Committee of the affiliated Bezmialem Vakıf University (approval no: E-54022451-050.04-194650, decision no: 2025/185, date: 24.05.2025).

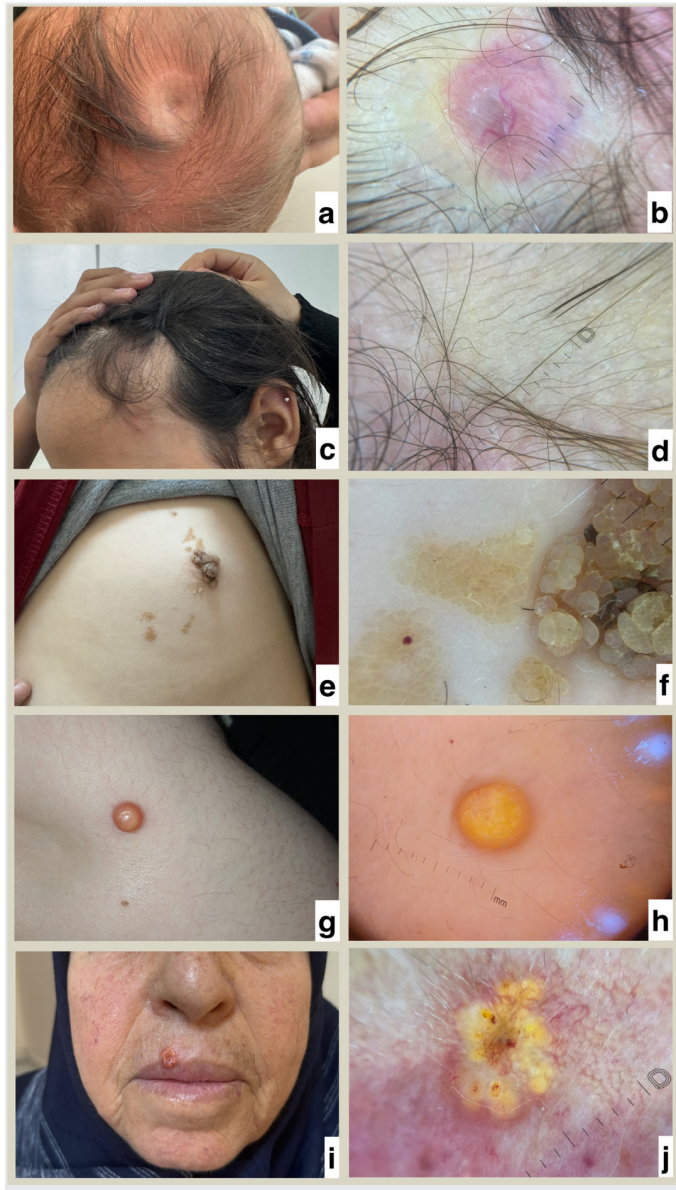

Figure 3. Clinical and dermoscopic appearances of conditions considered in the differential diagnosis of nevus sebaceus

Representative clinical (left column) and dermoscopic (right column) images of disorders excluded from the study but resembling nevus sebaceus are shown. *Aplasia cutis congenita* (a,b) presents as an atrophic alopecic plaque with a smooth shiny surface, with dermoscopy revealing a white structureless area and absence of follicular openings. Temporal triangular alopecia (c,d) appears as a triangular alopecic patch with preserved follicular openings, and dermoscopy demonstrates numerous vellus hairs on a normal scalp background. Epidermal nevus (e,f) presents as a papillomatous pigmented plaque, with dermoscopy showing brownish papillomatous structures and a cerebriform surface. Juvenile xanthogranuloma (g,h) is characterized by a dome-shaped yellow-orange papule, with dermoscopy revealing homogeneous yellow-orange areas and fine linear vessels. Nevoid sebaceous hyperplasia (i,j) manifests as a yellowish lobulated plaque, dermoscopically demonstrating enlarged yellow lobules with crown-like vessels

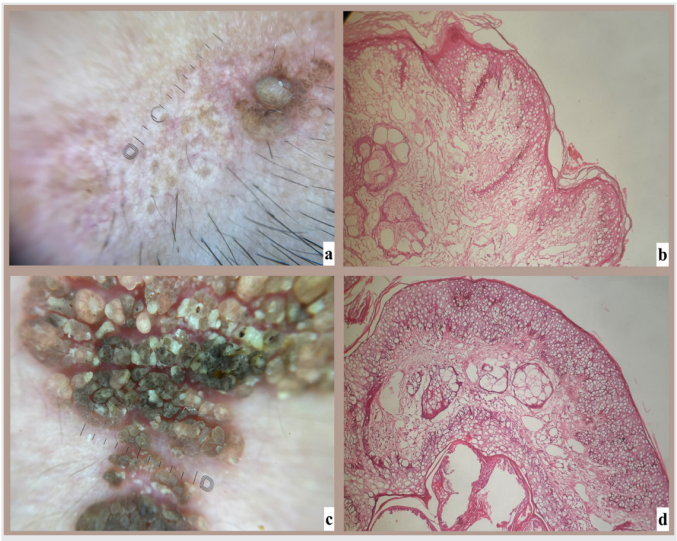

Figure 4. Dermoscopic-histopathological correlation in two representative cases of nevus sebaseus (NS)

(a) Dermoscopic image of a frontal lesion in a 23-year-old male in the early proliferative plaque stage revealing clustered yellowish globules on a pale background with partially preserved follicular openings. (b) Corresponding histopathology showing immature sebaceous lobules, dilated follicular infundibula, and mild acanthosis without papillomatosis, hallmarks of an early stage NS lesion. (c) Dermoscopic image of a neck lesion in a 16-year-old female at the verrucous stage demonstrating cerebriform, yellow-brown lobular structures with overlying whitish scaling, and complete loss of follicular openings. (d) Histological section confirming papillomatous epidermal hyperplasia, sebaceous gland hyperplasia, immature sebaceous units, and pronounced hyperkeratosis, indicative of a fully developed verrucous NS lesion

Statistical Analysis

Analyses were conducted in SPSS v29.0.2 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation and categorical variables as counts and percentages. Group comparisons of continuous variables (e.g., age across stages) used one-way analysis of variance (ANOVA) or independent-samples t-tests, as appropriate. Associations between categorical variables (dermoscopic features versus clinical stages) were examined with Fisher's exact test. Spearman's rank correlation assessed concordance between dermoscopic and histopathological features.

A post-hoc power analysis (G*Power 3.1.9.7) indicated that with n=25 the study had approximately 95% power to detect the strongest observed correlation (r=-0.64), about 73% power for a moderate effect (r≈0.50), and roughly 51% power for a smaller effect (r≈0.40) at two-sided α=0.05; an effect size of r≈0.535 would be required to achieve 80% power under these assumptions. No multiplicity adjustment was applied; therefore, p-values are interpreted cautiously in the context of multiple comparisons. Two-sided p<0.05 was considered statistically significant.

Results

Patient Demographics and Clinical Findings

A total of 25 patients (14 males, 11 females; mean age 17.9±11.9 years, range: 3-43) were included. Lesions were most frequently located on the scalp (60.0%), followed by the frontal/frontotemporal region (16.0%), the periauricular/postauricular area (16.0%), and the neck (8.0%). Clinical staging identified 7 patients (28.0%) in the infantile stage, 6 (24.0%) in the early proliferative plaque stage, 8 (32.0%) in the verrucous/late stage, and 4 (16.0%) in the nodular/late stage with neoplastic suspicion. Alopecia was present in over half of the patients, including cases with concomitant alopecia areata (AA). Associated comorbidities such as anxiety disorder, type 1 diabetes mellitus, hyperlipidemia, hypothyroidism, melasma, seborrheic dermatitis, and atopy were documented in several individuals. Detailed demographic and clinical data are summarized in Tables 1 and 2.

Dermoscopic Features

Stage-dependent dermoscopic patterns were observed (Table 3). Yellowish globules were significantly more frequent in early stages (100% vs. 50%, p=0.005), whereas grayish papillary structures were confined to advanced stages (0% vs. 50%, p=0.005). Lobulated yellow structures, fine linear/arborizing vessels, and brown globules tended to be more common in advanced stages; however, these differences did not reach statistical significance (p>0.05).

Histopathological Findings and Dermoscopy-histopathology Correlation

Histopathological evaluation was performed in more than half of the cohort. Although biopsy was performed in 15 patients, detailed histopathological data suitable for analysis were available for 13 patients, and these cases were included in the histopathological evaluation. Universal features included acanthosis, hyperkeratosis, basaloid proliferation, sebaceous hyperplasia, absence of terminal follicles, dilated infundibula, and perifollicular inflammation. Variable findings were papillomatosis (76.9%), immature/abortive hair follicles (92.3%), apocrine hyperplasia (30.8%), and eccrine hyperplasia (46.2%). Epidermal cysts and malignant transformation were not observed.

Correlation analysis did not reveal any statistically significant associations between dermoscopic and histopathological features (all p>0.05). Immature sebaceous glands were present in all specimens (13/13), precluding correlation analysis for this feature (Table 4).

Table 1. Patient demographics and clinical characteristics (n=25)

Variable	Value (n=25)
Age (mean ± SD, range)	17.9±11.9 years (3-43)
Sex	Male: 14 (56.0%), female: 11 (44.0%)
Lesion site	Scalp: 15 (60.0%); periauricular/postauricular: 4 (16.0%); frontal/frontotemporal: 4 (16.0%); neck: 2 (8.0%)
Clinical stage	Infantile stage (stage 1): 7 (28.0%); early proliferative plaque (stage 2): 6 (24.0%); verrucous/late-stage (stage 3): 8 (32.0%); nodular/late-stage with neoplastic suspicion (stage 4): 4 (16.0%)
Histopathological findings documented	13 (52.0%)
Presence of alopecia	14 (56.0%)
Presence of systemic comorbidities	9 (37.5%) [anxiety disorder (n=2), alopecia areata, type 1 DM, melasma, hyperlipidemia, hypothyroidism, atopy, seborrheic dermatitis]

Note: Values are presented as number (percentage) unless otherwise indicated
SD: Standard deviation, DM: Diabetes mellitus

Discussion

This retrospective study provides an integrated analysis of the clinical, dermoscopic, and histopathological features of 25 patients with NS evaluated over a two-and-a-half-year period. The mean age was 17.9±11.9 years (range: 3-43), with a slight male predominance (56.0%). Lesions were most frequently located on the scalp (60.0%), consistent with previous reports that attribute this predilection to the high density of sebaceous glands and embryological patterning of adnexal structures (17).

Clinical staging demonstrated a distribution across all maturational phases. Infantile lesions were identified in 7 patients (28.0%), early proliferative plaque lesions in 6 patients (24.0%), verrucous/late lesions in 8 patients (32.0%), and nodular/late lesions with early neoplastic suspicion in 4 patients (16.0%). One-way ANOVA confirmed a statistically significant difference in mean age across these stages ($F=3.18$, $p=0.045$), supporting the contribution of chronological age to lesion progression. However, the overlap in age ranges between groups indicates that staging also reflects intrinsic maturational processes, as emphasized in previous clinicopathological and dermoscopic series (18). Although no malignant transformations were detected, advanced-stage cases may represent cumulative proliferative remodeling, underscoring the importance of long-term follow-up in selected patients.

Localized alopecia was observed in more than half of the scalp NS cases, and two patients also had concomitant AA, illustrating the diagnostic challenges in pediatric alopecic plaques. NS can clinically resemble AA, and therefore requires careful differentiation (19). Experimental studies suggest that alopecia in NS may be related to elevated inhibitory cytokines, such as fibroblast growth factor 5, interleukin (IL)-4, IL-6, and DKK-1, which suppress hair growth pathways, including Wnt10b and lymphoid enhancer-binding factor 1 (20).

In our series, 40.0% of the lesions occurred at non-scalp sites, including the frontal, frontotemporal, auricular, and neck regions. These locations may mimic NSH; however, the presence of immature follicles and sebaceous hyperplasia remains distinctive for NS. Recent reports indicate that NSH can be misdiagnosed without histopathological confirmation (21), while early dermoscopic features, such as clustered yellow globules, may assist in differentiation (22). Our findings emphasize that non-scalp NS, although less frequent, requires the same level of diagnostic vigilance as certain lesions may closely mimic NS clinically, reinforcing the importance of histopathological confirmation, particularly in distinguishing it from NSH, epidermal nevus, or other adnexal proliferations in these regions.

Dermoscopy is valuable for staging NS by revealing stage-specific patterns that parallel lesion maturity. Early-stage lesions consistently displayed clustered yellowish globules on a pale background, reflecting immature sebaceous proliferation ($p=0.005$) (18,19). In contrast, advanced lesions were characterized by lobulated yellow structures with cobblestone or cerebriform patterns, brown globules, and more frequent arborizing vessels, although these differences did not reach statistical significance ($p>0.05$) (23,24). Grayish papillary structures were observed exclusively in advanced lesions ($p=0.005$), underscoring their diagnostic relevance (16). Taken together, our findings support the concept that staging reflects intrinsic maturational processes of the lesion rather than chronological age, likely driven by pubertal hormonal influence, RAS/MAPK-mediated sebaceous proliferation, and the local cytokine-inflammatory microenvironment (6,25). Although malignant transformation was not observed in our series, previous reports documented secondary tumors such as sebaceoma with carcinomatous change, poroma, and trichoblastoma arising within NS, highlighting the importance of continued vigilance in advanced stages (26,27).

Table 2. Detailed demographic and clinical characteristics of individual patients

Case	Age	Sex	Localization	Clinical stage	Histopathology	Management (treatment/follow-up)	Associated comorbidities
1	9	M	Periauricular	Verrucous/late-stage NS	Not performed	Follow-up	-
2	37	F	Scalp	Verrucous/late-stage NS with early neoplastic suspicion	Performed	Excisional biopsy	Anxiety disorder
3	19	F	Frontal	Early proliferative plaque stage	Performed	Shave biopsy	Melasma
4	7	M	Scalp	Infantile stage	Not performed	Follow-up	Alopecia areata
5	34	F	Frontotemporal	Verrucous/late-stage NS with early neoplastic suspicion	Performed	Excisional biopsy	Type 1 DM, alopecia areata
6	13	F	Frontal	Verrucous/late-stage NS	Performed	Excisional biopsy	-
7	16	F	Neck	Verrucous/late-stage NS	Performed	Excisional biopsy	-
8	23	M	Frontal	Early proliferative plaque stage	Performed	Excisional biopsy	-
9	14	M	Scalp	Infantile stage	Performed	Excisional biopsy	-
10	10	M	Scalp	Infantile stage	Performed	Punch biopsy	-
11	18	F	Postauricular	Verrucous/late-stage NS	Performed	Shave biopsy	-
12	9	F	Scalp	Infantile stage	Not performed	Follow-up	-
13	43	M	Scalp	Verrucous/late-stage NS with early neoplastic suspicion	Performed	Excisional biopsy	Anxiety disorder
14	18	F	Scalp	Early proliferative plaque stage	Not performed	Follow-up	-
15	9	M	Scalp	Infantile stage	Performed	Excisional biopsy	-
16	41	M	Scalp	Verrucous/late-stage NS	Performed	Excisional biopsy	Hyperlipidemia
17	3	M	Scalp	Infantile stage	Performed	Punch biopsy	-
18	16	M	Scalp	Early proliferative plaque stage	Not performed	Follow-up	-
19	21	M	Scalp	Infantile stage	Not performed	Follow-up	Seborrheic dermatitis
20	10	F	Scalp	Early proliferative plaque stage	Not performed	Follow-up	-
21	11	M	Postauricular	Verrucous/late-stage NS	Not performed	Follow-up	-
22	40	F	Neck	Verrucous/late-stage NS	Performed	Excisional biopsy	Hypothyroidism
23	7	M	Scalp	Early proliferative plaque stage	Not performed	Follow-up	Atopy
24	14	M	Postauricular	Verrucous/late-stage NS	Performed	Shave biopsy	-
25	6	F	Scalp	Early proliferative plaque stage	Not performed	Follow-up	-

Note: Table presents individual patient-level data including age, sex, lesion localization, clinical stage, histopathological status, management, and associated comorbidities
NS: Nevus sebaceus, DM: Diabetes mellitus

Table 3. Association between dermoscopic features and clinical stages of nevus sebaceus (n=25)

Dermoscopic feature	Early stages (1-2) (n=13)	Advanced stages (3-4) (n=12)	Fisher's exact test (p-value)
Yellowish globules	13/13 (100.0%)	6/12 (50.0%)	**0.005**
Lobulated yellow structures	8/13 (61.5%)	10/12 (83.3%)	0.378
Fine linear/arborizing vessels	4/13 (30.8%)	8/12 (66.7%)	0.115
Grayish papillary structures	0/13 (0.0%)	6/12 (50.0%)	**0.005**
Brown globules	4/13 (30.8%)	8/12 (66.7%)	0.115

Note: Frequencies were compared between early-stage (stages 1-2, n=13) and advanced-stage (stages 3-4, n=12) lesions using two-sided Fisher's exact test. P<0.05 was considered statistically significant

Table 4. Variable histopathological features in nevus sebaceus and their dermoscopic associations (n=13 biopsy cases)

Histopathological feature	Frequency n (%)	Dermoscopic association	Spearman r	p-value	Comment
Papillomatosis	10 (76.9)	Yellowish globules	0.43	0.147	NS
Immature/abortive HF	12 (92.3)	Yellowish globules	0.43	0.139	NS
Apocrine hyperplasia	4 (30.8)	Grayish papillary structures	-0.08	0.787	NS
Eccrine hyperplasia	6 (46.2)	Lobulated yellow structures	-0.46	0.113	Negative trend, NS
Immature sebaceous glands	13 (100)	Lobulated yellow structures	NA	NA	All cases positive

Note: Universal histopathological features present in all analyzed specimens were omitted from the table. Spearman correlation coefficients are two-sided
NS: Not significant, HF: Hair follicle, NA: Not applicable

Histopathological evaluation in our cohort showed consistent features of NS—acanthosis, basaloid proliferation, hyperkeratosis, immature sebaceous glands with sebaceous hyperplasia, dilated infundibula, absence of terminal follicles, and perifollicular inflammation—findings that were nearly universal and concordant with large series (28). The lack of normal terminal follicles relative to adjacent skin is a practical diagnostic clue, while the presence of mature sebaceous lobules arranged around a dilated duct underscores the hamartomatous nature of NS rather than simple sebaceous hyperplasia (29). Consistent with a recent study of 60 cases by Karimian et al. (30), our histopathological evaluation confirmed papillomatosis (76.9%), immature/abortive hair follicles (92.3%), and apocrine hyperplasia (30.8%) as frequent features of NS.

While we also observed eccrine hyperplasia (46.2%), no malignant transformation was detected in our series. Although correlation analysis did not reveal statistically significant dermoscopy-histopathology associations, this was likely related to the intrinsic heterogeneity of NS and maturational variation within different regions of the same lesion, which produces stage-dependent dermoscopic appearances rather than direct microscopic counterparts, as well as the limited number of biopsied lesions, which may have reduced statistical power. Reported malignant risk remains variable, with some series noting higher rates in older patients (31,32), whereas others advocate individualized, risk-adapted management (33).

The cobblestone or cerebriform brown globules observed in advanced lesions likely reflect underlying epidermal remodeling and papillomatosis, consistent with prior case-based correlations (16).

In our cohort, most patients (60%) underwent surgical procedures for diagnostic or therapeutic purposes, predominantly in adult cases, reflecting our institutional tendency to prioritize operative management in this age group. While no malignant transformations were observed, surgical removal was considered the preferred approach for lesions showing progressive morphological changes or occurring in adulthood. Histopathological evaluation should ideally include multipoint sampling, as NS may harbor heterogeneous adnexal proliferations, especially in longstanding lesions (26,27). The literature on NS management remains divided: observation in children with excision deferred to adulthood has been suggested, and large pediatric cohorts have reported no malignancy, supporting conservative monitoring (34). Universal excision has also been recommended (35), whereas a large metaanalysis emphasized individualized, riskadapted strategies (33). Imagingassisted decisionmaking with dermoscopy and, when available, reflectance confocal microscopy has been proposed (23,24), and surveys have further highlighted variability between dermatologists and surgeons regarding the timing of excision (36). Prophylactic excision is also supported by narrative reviews (28).

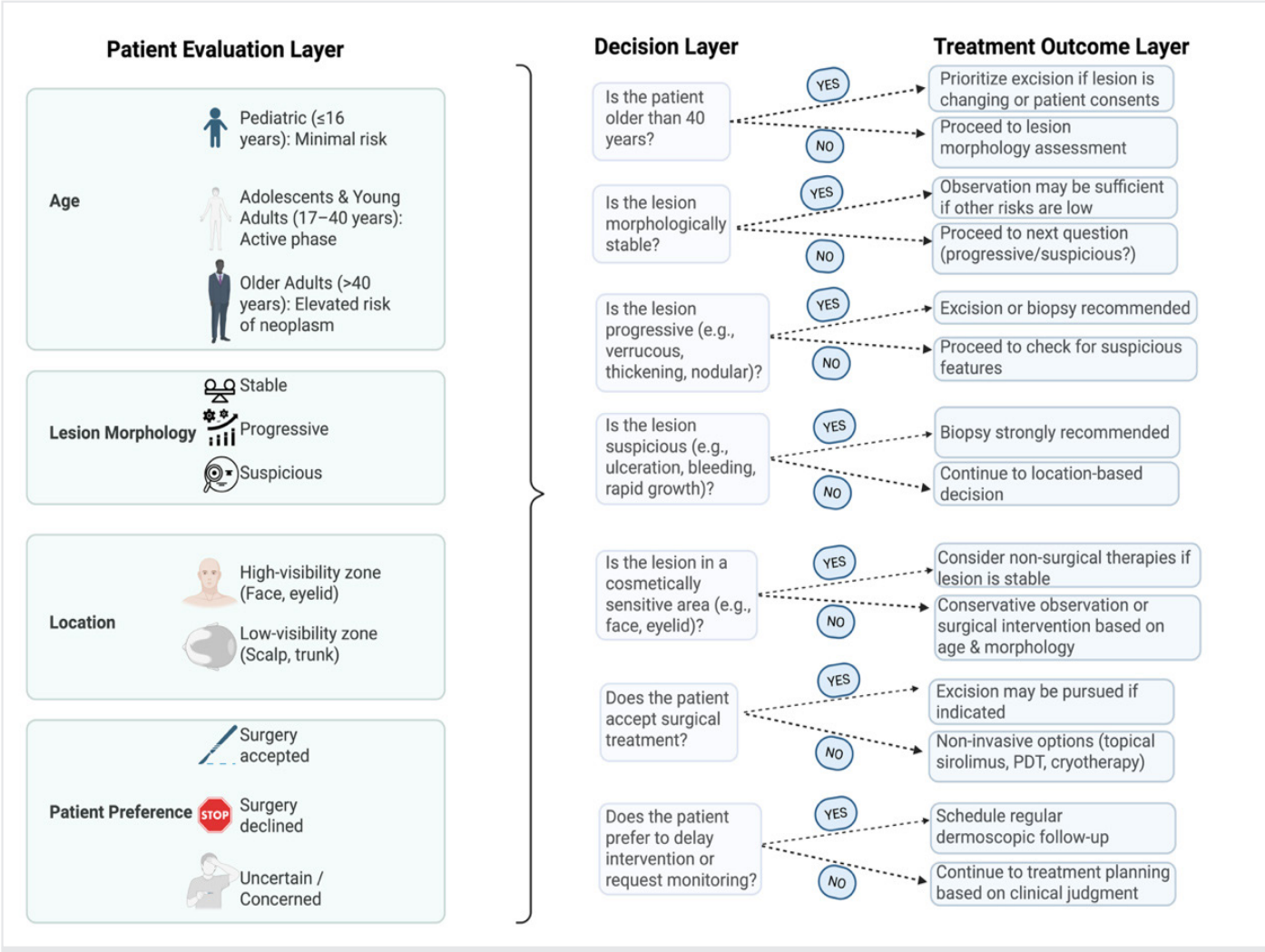

Figure 5. Individualized management flowchart for nevus sebaceus (NS)

This three-tiered clinical decision model integrates patient-specific variables (age, lesion morphology, location, and preference), guiding personalized treatment strategies for NS. The decision layer consists of sequential clinical questions leading to evidence-based management options. Final outcomes include surgical excision, observation, or non-invasive therapies (e.g., topical sirolimus, photodynamic therapy, cryotherapy). The algorithm emphasizes shared decision-making, cosmetic considerations, and malignancy risk stratification across life stages.

PDT: Photodynamic therapy

Non-surgical approaches, including topical sirolimus (37), photodynamic therapy (38), carbondioxide laser ablation (39-42), and cryotherapy (43,44), have been reported, although longterm efficacy remains uncertain. Overall, our findings support selective follow-up for stable lesions, with surgery prioritized in advanced or clinically suspicious cases. This approach is captured in our management algorithm (Figure 5), which integrates patient age, lesion morphology, and treatment preference and is contextualized within the range of strategies summarized in Table 5.

Study Limitations

The retrospective nature of this study and the short follow-up period may limit the evaluation of the long-term outcomes and generalizability. Further prospective studies incorporating molecular analyses and comparative treatment groups along with extended follow-up would provide deeper insights and validate our findings.

Table 5. Management strategies for nevus sebaceus: literature-based comparative overview

Author(s)	Patient population/ sample size	Primary recommendation	Key rationale	Alternative approaches
Santibanez-Gallerani et al. (34)	757 pediatric patients	Excision not necessary	No malignancy found; age-related risk emphasized	Regular monitoring
Rosen et al. (35)	631 patients (651 NS lesions)	Universal excision	BCC observed in 0.8% of patients, including children; no clinical predictors; premalignant lesions in 1.1%	Flexible timing; shared decision-making encouraged
Pang et al. (33)	Meta-analysis of 6005 cases	Risk-stratified, individualized approach	2.4% malignant transformation; 1.7% BCC; 10.3% benign tumors	Excision or observation depending on case specifics
Zaballos et al. (24)	58 lesions with histology + dermoscopy	Imaging-assisted decision-making	Challenging dermoscopic distinction between BCC and TB	Confocal microscopy, selective biopsy
Wali et al. (36)	National survey (UK dermatologists & surgeons)	Expert opinion divided	90% of surgeons vs. 30% of dermatologists recommend excision	Majority of dermatologists favor clinical follow-up
Neto et al. (1)	Narrative review	Prophylactic excision favored	Cosmetic concerns, secondary neoplasm potential, trauma-induced changes	Laser ablation, dermabrasion, PDT
Zhou and Antaya (37)	5 cases with clinically confirmed NS	Topical sirolimus	Significant lesion flattening; minimal side effects	Non-invasive topical therapy
Moreno-Arrones and Perez-Garcia (38)	6 patients with facial NS	PDT	Up to 80% lesion reduction; long-term stability; no recurrence	Surgery deferred; good cosmetic outcome
Kim et al. (39); Sutedja et al. (40); Dartaha and Jobran (41); Gaydina et al. (42)	5 young patients (ages 10-30)	CO_2 laser ablation (± isotretinoin)	Effective for small-to-moderate lesions, including facial and atypical locations; cosmetically favorable; no short-term recurrence; requires long-term follow-up	Full-thickness excision; close observation for recurrence or secondary neoplasia
Alqahtani and Al-Natour (43); Handler and Schwartz (44)	16-year-old patient with trichilemmoma; literature-based technical protocol	Cryotherapy	Cosmetically favorable for patients declining surgery; recommended for superficial lesions; effective with proper freeze technique	Full-thickness excision; laser ablation; clinical follow-up for recurrence
Kaya et al. (present study)	25 patients; 10 followed non-invasively	Selective follow-up appropriate	No malignant transformation observed; short-term stability in conservatively managed lesions	Dermoscopic surveillance; biopsy if clinical change

Note: Summary of literature-based management approaches for nevus sebaceus
PDT: Photodynamic therapy, BCC: Basal cell carcinoma, TB: Trichoblastoma, NS: Nevus sebaceus

Conclusion

Although no statistically significant dermoscopic-histopathological associations were identified, our study demonstrated that dermoscopy provided robust, stage-dependent diagnostic insights in NS. These findings emphasize that dermoscopic patterns mirror the biological evolution of the lesion, supporting its use as a non-invasive tool for risk stratification and follow-up. The absence of malignant transformation in this cohort is consistent with the indolent nature of NS, yet long-term vigilance remains warranted. Conservative surveillance may be justified in selected cases, but surgical excision continues to represent the standard approach for advanced or clinically suspicious lesions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Scientific Research Ethics Committee of the affiliated Bezmialem Vakıf University (approval no: E-54022451-050.04-194650, decision no: 2025/185, date: 24.05.2025).

Informed Consent: This retrospective observational study was conducted at Nizip State Hospital, a public secondary care center in Gaziantep, Türkiye, over a 2.5-year period (2023-2025).

Acknowledgments

Throughout the course of this study, we adhered strictly to the World Medical Association Declaration of Helsinki and the Good Clinical and Laboratory Practice standards. All figures were created using BioRender.com under an academic license for scientific communication purposes.

Footnotes

Authorship Contributions

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

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

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Data Availability Statement

The datasets analyzed during the current study are not publicly available due to institutional data protection policies, but are available from the corresponding author upon reasonable request.

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Case Report

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Recurrent Facial Palsy and Fissured Tongue in an Adolescent: A Case of Melkersson-Rosenthal Syndrome

Ergenlik Döneminde Tekrarlayan Yüz Felci ve Fissürlü Dil: Melkersson-Rosenthal Sendromu Olgusu

Hasan Burak KAYACI[1], Celal ŞALÇİNİ[2]

[1]Üsküdar University Faculty of Medicine, Department of Neurology, İstanbul, Türkiye
[2]NPİstanbul Brain Hospital, Clinic of Neurology, İstanbul, Türkiye

ABSTRACT

Melkersson-Rosenthal syndrome (MRS) is a rare neuromucocutaneous disorder characterized by recurrent facial palsy, orofacial swelling, and fissured tongue (lingua plicata). This case report presented a 16-year-old male who experienced his fourth episode of sudden-onset unilateral facial paralysis. Neurological examination revealed lower motor neuron-type facial weakness and a markedly enlarged tongue with deep fissures. Laboratory tests and imaging studies, including brain magnetic resonance imaging and systemic evaluations, were all within normal limits. Based on the presence of the classic clinical triad and the exclusion of other potential causes, a diagnosis of MRS was made. The patient responded well to corticosteroid therapy.

Keywords: Melkersson-Rosenthal syndrome, recurrent facial nerve palsy, lingua plicata, orofacial granulomatous disease

ÖZ

Melkersson-Rosenthal sendromu (MRS), tekrarlayan yüz felci, orofasiyal şişlik ve fissürlü dil (lingua plicata) ile karakterize, nadir görülen nöromukokutanöz bir hastalıktır. Bu olgu sunumunda, dördüncü kez ani başlayan tek taraflı yüz felci atağı yaşayan 16 yaşındaki bir erkek hasta sunuldu. Nörolojik muayenede alt motor nöron tipinde yüz felci ve derin fissürlere sahip bir dil saptandı. Beyin manyetik rezonans görüntülemesi ve sistemik değerlendirmeleri de dahil olmak üzere laboratuvar testleri ve görüntüleme incelemeleri normal sınırlarda bulundu. Klasik klinik üçlü belirtinin varlığı ve diğer olası nedenlerin dışlanmasıyla MRS tanısı kondu. Hasta, kortikosteroid tedavisine iyi yanıt verdi.

Anahtar Kelimeler: Melkersson-Rosenthal sendromu, tekrarlayan fasiyal sinir felci, fissürlü dil, orofasiyal granülomatöz hastalık

Introduction

Melkersson-Rosenthal syndrome (MRS) is a rare neuromucocutaneous disorder, typically characterized by recurrent facial palsy, facial or lip swelling, and lingua plicata. Fewer than a third of patients present with all three symptoms and in most cases, symptoms occur progressively or partially (1-3).

The condition often begins in childhood or adolescence and follows a relapsing-remitting course. Swelling may resolve within hours or days initially, but may later become more persistent and even permanent due to granulomatous lymphatic obstruction. Meanwhile, facial palsy episodes are often temporary but may recur. Lingua plicata is usually asymptomatic and detected on physical examination (3,4).

Although the etiology is unclear, proposed causes include genetic predisposition, familial clustering and possible chromosomal associations, immune dysregulation, and associations with Crohn's disease, sarcoidosis, or orofacial

Address for Correspondence: Res. Assist. Hasan Burak Kayacı, Üsküdar University Faculty of Medicine, Department of Neurology, İstanbul, Türkiye
E-mail: hasanburakkayaci@gmail.com
ORCID IDs of the authors: H.B.K.: 0009-0000-3956-3335, C.Ş.: 0000-0002-4489-4400

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granulomatosis triggered by hormonal changes have been reported in studies (5).

Diagnosis is made clinically, supported by ruling out infectious, neoplastic, or demyelinating causes. Imaging findings are typically normal, though in rare cases granulomatous inflammation may be detected (6).

Treatment is symptomatic. Systemic corticosteroids are generally the first line of therapy, while immunosuppressants or biologics like methotrexate or anti-tumor necrosis factor agents are considered in chronic or recurrent cases (3,6). Surgical intervention is rarely required but may be considered for cosmetic deformity or chronic edema (2,6).

Case Report

A 16-year-old male presented with left-sided facial palsy, which had developed suddenly over the course of one day. This was his fourth episode of unilateral facial weakness within the past three years. Each episode had previously responded well to a short course of corticosteroids, with near-complete recovery. He reported no other systemic symptoms, no recent infections, trauma, or vaccination.

Neurological examination revealed lower motor neuron-type facial weakness, impaired eye closure, and asymmetry of the mouth. Additionally, his tongue appeared firm, enlarged, and showed characteristic deep fissures (lingua plicata) (Figure 1).

Laboratory studies including vasculitis panel, acute phase reactants, and viral serologies (herpes simplex virus, Epstein-Barr virus, cytomegalovirus) were all within normal limits. Magnetic resonance imaging (MRI) of the brain and brainstem, as well as MRA, revealed no structural or inflammatory abnormalities. A chest computed tomography and gastrointestinal consultation were conducted to evaluate for systemic granulomatous diseases; both were normal.

The clinical triad of recurrent facial nerve palsy, orofacial swelling, and fissured tongue led to the diagnosis of MRS, a rare granulomatous disorder characterized by the classic triad of orofacial swelling, recurrent facial palsy, and fissured tongue (2,6).

Informed consent was obtained from the participant for the study.

Discussion

MRS should be suspected in adolescents with recurrent facial palsy, especially when accompanied by lip/tongue swelling or fissured tongue. A normal MRI and laboratory work-up help exclude mimics such as multiple sclerosis, vasculitis, or infectious cranial neuritis.

Our patient displayed all Bell's palsy diagnostic criteria along with fissured tongue. The wide range of conditions which may present as MRS includes thyroid orbitopathy and allergic reactions and angioedema and bacterial and viral and filarial infections and systemic lupus erythematosus and dermatomyositis and Bell's palsy itself and Ramsay Hunt syndrome (7). This situation didn't require a biopsy to confirm MRS diagnosis because all classic signs were present. The oral manifestations of Crohn's disease and other inflammatory bowel diseases include lip swelling with fissures as well as mucositis and gingivitis and glossitis and the characteristic cobblestone appearance of oral mucosa (8). The available scientific evidence indicates that abnormal immune responses along with immune system imbalances and allergic tendencies affect people who develop MRS. The current medical literature does not identify any definitive treatment for this condition despite its management using short-term immunosuppressive medication (8). Medical practitioners use corticosteroids as initial treatment for MRS by administering them through injection into the lesion or systemically while decreasing medication doses over 3-6 weeks based on patient symptoms. Research shows that corticosteroid treatment leads to symptom improvement in 50-80% of patients while reducing the chance of reoccurrence to 60-75% (9). The treatment plan for this patient included methylprednisolone medication together with eye care for the affected side and physical therapy for

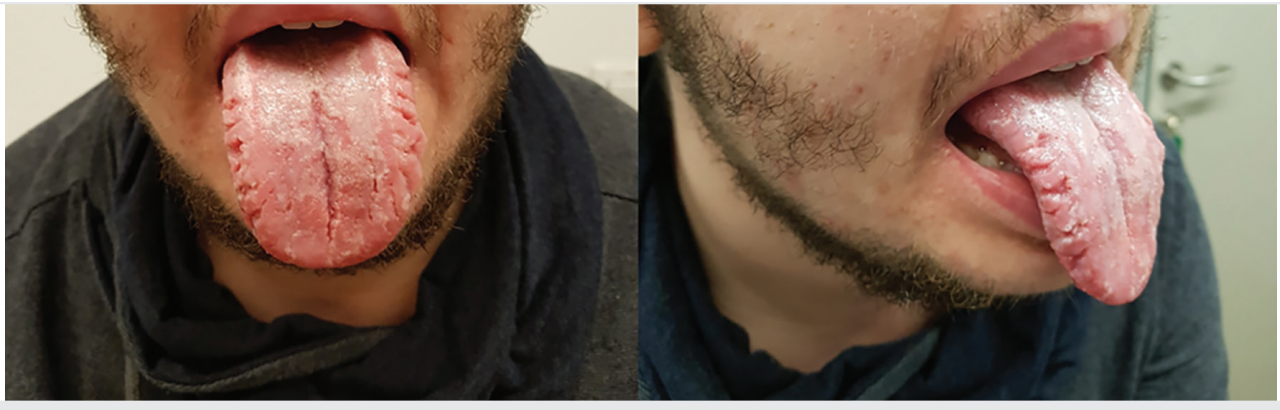

Figure 1. Characteristic deep fissures of the tongue (lingua plicata)

facial palsy rehabilitation. The symptomatic treatment of eye care benefits from additional vitamins such as thiamine and niacin and riboflavin and pyridoxine and ascorbic acid and vitamin E. The treatment requires daily lubricating drop applications combined with overnight protective eye pad use because the eye can't be closed completely. The recovery of facial palsy benefits from physical therapies that include exercise together with biofeedback and electrotherapy and massage and thermotherapy.

Ethics

Informed Consent: Informed consent was obtained from the participant for the study.

Footnotes

Authorship Contributions

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

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Review

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Evaluation of Tissue Oxygenation Using Near-infrared Spectroscopy and Nursing Care in Newborns: A Review of the Literature

Yenidoğanlarda Yakın Kızılötesi Spektroskopi ile Doku Oksijenasyonunun Değerlendirilmesi ve Hemşirelik Bakımı: Literatür Derlemesi

Hande ÖZGÖRÜ[1], Suzan YILDIZ[2]

[1]Süleyman Demirel University, Health Services Vocational School First and Emergency Aid Program, Isparta, Türkiye
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Florence Nightingale Faculty of Nursing, Department of Child Health and Diseases Nursing, İstanbul, Türkiye

ABSTRACT

Term and preterm newborns are exposed to many invasive procedures in the neonatal intensive care unit (NICU). During these procedures, preterms face many complications, especially respiratory system and gastrointestinal tract complications, since they do not complete their systemic development. Near-infrared spectroscopy (NIRS) is used in the diagnosis and treatment of these problems. It is an up-to-date application that evaluates the effectiveness of various non-pharmacologic interventions. At the same time, NIRS is a research technique that uses the absorption and reflection of a near-infrared light spectrum to measure tissue oxygenation, indirectly representing regional blood flow. Currently, it is possible to simultaneously measure regional oxygenation in multiple areas of the body, including the brain, kidney, and abdominal circulation. Regional (cerebral, abdominal) tissue oxygen saturation measured using NIRS has become an increasingly used parameter in the monitoring of cerebral hemodynamics in newborns, in the diagnosis and treatment of gastrointestinal tract complications such as nutritional intolerance and necrotizing enterocolitis. When the literature is examined, it is seen that studies on NIRS focus on cerebral oxygenation in preterm newborns. It is very important for nurses working in the NICU to use NIRS devices, know the points to be considered in follow-up, and learn how to

ÖZ

Yenidoğan yoğun bakım ünitesinde (YYBÜ) term ve preterm yenidoğanlar birçok invaziv işleme maruz kalmaktadır. Bu işlemler sırasında özellikle pretermler sistemsel gelişimlerini tamamlamadıkları için solunumsal ve gastrointestinal sistem başta olmak üzere birçok sistemle ilgili komplikasyonlar ile karşı karşıyadır. Bu sorunların tanılama ve tedavi aşamasında kullanılan near-infrared spectroscopy (NIRS) (yakın kızılötesi spektroskopi) cihazı, çeşitli non-farmakolojik girişimlerin etkinliğini değerlendiren güncel bir uygulamadır. Aynı zamanda NIRS, doku oksijenasyonunu ölçmek için yakın kızılötesi bir ışık spektrumunun emilimini ve yansımasını kullanan ve dolaylı olarak bölgesel kan akışını temsil eden bir araştırma tekniğidir. Şu anda, beyin, böbrek ve abdominal dolaşım da dahil olmak üzere vücudun birden fazla bölgesinde bölgesel oksijenasyonu aynı anda ölçmek mümkündür. NIRS ile ölçülen bölgesel (serebral, abdominal) doku oksijen doygunluğu, yenidoğanlarda serebral hemodinamiklerin izlenmesinde, beslenme intoleransı, nekrotizan enterokolit gibi gastrointestinal komplikasyonların tanı ve tedavisinde kullanımı artan bir parametre haline gelmiştir. Literatüre bakıldığında NIRS ile ilgili yapılan çalışmaların preterm yenidoğanlarda serebral oksijenizasyon üzerine yoğunlaştığı görülmektedir. YYBÜ'nde çalışan hemşirelerin NIRS cihazını kullanması, takibinde dikkat etmesi gereken noktaları

Address for Correspondence: Hande Özgörü PhD, İstanbul University-Cerrahpaşa, Institute of Graduate Education, Department of Child Health and Diseases Nursing Doctoral Program, İstanbul, Türkiye
E-mail: ozgoruhande93@gmail.com
ORCID IDs of the authors: H.Ö.: 0000-0002-9263-8372, S.Y.: 0000-0002-2528-2185

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ABSTRACT

interpret them in order to identify complications at an early stage. The purpose of this literature review was to evaluate the information on the measurement of cerebral and abdominal tissue oxygenation in newborns using NIRS technology and nursing care in light of current literature.

Keywords: Nursing care, near-infrared spectroscopy, newborn

ÖZ

bilmesi ve yorumlanmasını öğrenmesi komplikasyonların erken dönemde tanımlanması açısından oldukça önemlidir. Bu literatür derlemesindeki amaç; yenidoğanlarda serebral ve abdominal doku oksijenizasyonunun NIRS teknolojisi ile ölçülmesine yönelik bilgileri ve hemşirelik bakımını güncel literatür ışığında değerlendirmektir.

Anahtar Kelimeler: Hemşirelik bakımı, yakın kızılötesi spektroskopi, yenidoğan

Introduction

Near-infrared spectroscopy (NIRS) devices were first used in medical research by Jöbsis (1) in the 1970s and have been shown to be a non-invasive technique that monitors regional tissue oxygenation [the percentage of oxyhemoglobin (HbO_2) and deoxyhemoglobin (HbR) (regional oxygen saturation: HbO_2/HbO_2+HbR) concentration in tissues] reflecting the perfusion status (2,3). In doing so, it uses the absorption and reflection of a near-infrared light spectrum (light with a wavelength of 700-1000 nm) (4,5).

This technique is used to assess cerebral and abdominal tissue oxygen saturation in various disease states of preterm and term neonates to monitor cerebral hemodynamics, increase awareness of abnormal perfusion status, potentially reduce the risks associated with many diseases that can lead to ischemic injury, provide data in the diagnosis and treatment of gastrointestinal tract complications such as nutritional intolerance, necrotizing enterocolitis (NEC), and improve the effectiveness of various non-pharmacologic interventions. It is preferred to provide data on treatment and evaluation of the effectiveness of various non-pharmacological interventions (6-9). It is also increasingly used to measure tissue oxygenation in other organs and determine blood flow. Today, with the NIRS technique, it is possible to measure regional oxygenation simultaneously and continuously in many parts of the body, including the brain, intestine, kidney, pulmonary, muscle, peripheral and liver circulation, without interrupting routine care (10-12). However, more research is needed to establish universal normative data based on cerebral and abdominal oxygenation in newborns. The use of different devices, follow-ups at different ages, the inadequacy of studies especially in preterm and term newborns, and the use of different optical probes and algorithms by device manufacturers limit the widespread clinical application of the device (6).

Regions Where NIRS is Used in Newborns

In newborns, the NIRS is often used in the cerebral and abdominal regions.

Cerebral NIRS: This can help identify and treat cerebral injuries related to regional perfusion and ischemia, primarily intraventricular hemorrhage and white matter injury (4). Preterms, due to their underdeveloped cerebral autoregulation system, are unable to provide sufficiently consistent cerebral blood flow in the face of stressors (13). NIRS can help continuously monitor regional brain tissue perfusion and obtain clear data on the balance between oxygen use and requirement (3). In addition, because acute fluctuations in partial arterial carbon dioxide pressure ($PaCO_2$) are associated with fluctuations in cerebral blood flow, the use of NIRS in mechanically ventilated severely preterm patients may guide detecting and correcting these changes before damage occurs (14). If the cerebral NIRS value remains below 40-45% in a short period of time, such as 30 minutes, it may have negative effects on cerebral blood flow and brain development (3,4).

Although the specific values differ in various NIRS devices, cerebral regional oxygen saturation is generally lower than abdominal oxygenation (splanchnic/somatic) because the brain has more metabolic activity and consumes more oxygen (15). Factors that affect the accuracy of measurements include the placement of sensors in different parts of the forehead, the shape of the forehead, extracranial structures, blood flow, and the depth of the brain surface (6).

Abdominal NIRS technique: In newborns, the abdominal region is the area used to monitor oxygenation of the kidney, liver, and intestine. It is known that abdominal oxygenation values are closely related to changes in superior mesenteric artery blood flow (7). For this reason, healthy preterms may experience a decrease in abdominal oxygenation values in the first weeks of life and an increase in the following weeks (3,15).

The locations where the probe is placed for cerebral and abdominal oxygenation monitoring are given in Table 1 (3,16,17).

Interpretation of NIRS measurements: The tissue oxygenation index reference range of newborns is expected to vary between 55-85% depending on many factors such as clinical status and postnatal age. However, the universally accepted reference range remains unclear (18). There are also situations that create difficulties in the interpretation of regional oxygenations, including variations in devices and probes, gestational week, and deficiencies in universal normative values (19).

Table 1. Positioning locations of the NIRS probe in newborns

Cerebral NIRS probe	Abdominal NIRS probe
• Middle frontal • Left frontoparietal • Right frontoparietal *Simultaneous monitoring can be done with right and left dual probes	**Kidneys** • Right retroperitoneal region • Left retroperitoneal region **Intestines** • Lower right quadrant • Lower left quadrant • Umbilicus **Liver** • Upper right quadrant

NIRS: Near-infrared spectroscopy

Because NIRS devices can monitor oxygenation in different regions at the same time, it has been stated that interpreting measurements with regional proportioning can give more accurate information about different tissue oxygenation to certain organs (20,21). Cerebro-splanchnic oxygenation ratio values below 0.75 are associated with an increased risk of mesenteric ischemia (2,8,20). However, studies have shown that the splanchnic-cerebral oxygenation (SCOR) ratio is between 1.02 and 1.61, which can be seen as a signal of an increased risk of mesenteric ischemia (11,22). There was no correlation between SCOR and gestational age in healthy term newborns, but a positive correlation was found with postnatal clock, and it was shown that its value might be lower than normal in the first days of life (23). It has also been reported that the rate of abdominal oxygenation and SCOR decreases during enteral feeding in anemic preterm neonates (8), and that NEC discrimination cannot be made when abdominal and cerebro-splanchnic oxygenation rates are monitored in preterm newborns with acute gastrointestinal symptoms (24). It has been stated that SCOR elevations may confirm the diagnosis and frequent variability in splanchnic oxygenation can exclude NEC in preterm NEC (22).

Uses of NIRS

According to the regions where NIRS is used in term and preterm newborns, the functions and areas where NIRS is used are gradually increasing. In the literature, NIRS has been used in the planning of diagnosis, follow-up, treatment, and care, as well as in determining the effect of different applications such as smell, music, sleep, and position on oxygenation levels (10,25).

Clinical and Research Results

Areas Where Cerebral NIRS is Used

Diagnosis, follow-up, treatment, and care planning: Cerebral oxygenation monitoring in the delivery room and after delivery may be useful in stabilizing newborns (26,27), providing information about changes in hemodynamics, and especially when used in conjunction with other neuromonitoring tools (28). For this reason, it has been stated that pulse oximetry is a complementary approach and can be used routinely to determine oxygen demand in newborns quickly and accurately (29). It is thought that changes in cerebral oxygen saturation may be effective in providing information about the state of cerebral blood flow or general brain health, in the planning of care by healthcare professionals during high-risk procedures such as cardiopulmonary bypass (15), and monitoring major organ perfusion (such as cerebral, renal, intestinal) adequacy in children, infants, and newborns (9). Monitoring cerebral oxygenation with a predetermined treatment algorithm has been shown to reduce the amount of cerebral hypoxia in extremely preterm infants (26). It has been used in the treatment of neonates undergoing cardiac surgery (6), and has been found to be significantly lower in neonates with cyanotic and acyanotic heart lesions, and follow-up can be combined with arterial blood pressure monitoring, a continuous dynamic assessment of autoregulation at the bedside. It has been reported that it will provide the possibility to identify times of impaired autoregulation and initiate appropriate measures to increase, decrease, or maintain adequate cerebral blood flow (3). Thus, it is possible to reduce brain damage such as intraventricular hemorrhage or periventricular leukomalacia and facilitates the rational use of inotropes (3,26).

In the first 24 hours following hypoxic ischemia, significantly elevated cerebral oxygenation and decreased cerebral fractional oxygen extraction values are observed (30). This condition is thought to be caused by a combination of increased cerebral perfusion, impaired cerebral autoregulation, and less oxygen use. Therefore, the concomitant use of NIRS with amplitude-integrated in neonates receiving treatment for therapeutic hypothermia has been shown to be useful in determining the prognosis (4,30,31). In newborns treated for hypothermia, follow-up with combined tools is critical for the first 72 hours, especially between 18 and 60 hours (32).

Newborns hospitalized in the neonatal intensive care unit (NICU) are especially exposed to pain and stress. Long-term or frequent pain experience can have a variety of negative effects in newborns in the short and long term, such as

affecting the development and growth of the brain and senses. If pain is not reduced or eliminated with effective approaches, it can cause neurologic or behavioral disorders over time. Cerebral NIRS, an approach that evaluates brain activity in response to stressful and painful stimuli in newborns, is proposed. In this direction, it is stated that applications such as kangaroo care, position changes, and sucrose administration in painful procedures reduce pain and positively affect brain oxygenation (25).

In positioning applications: The NIRS device is an important tool for assessing processes that alter cerebral oxygenation due to significant venous drainage impairment (26). It has been shown that in adult patients at risk of high cerebral pressure due to traumatic brain injury the head and neck are routinely placed in a neutral position to facilitate venous drainage, and in term neonates, when the head is positioned to one side, it functionally inhibits jugular venous drainage on the same side. Accordingly, impaired venous drainage and decreased cerebral tissue oxygenation have been reported to be among the factors that play a role in intraventricular hemorrhage (33). Early head positioning in the midline in preterm treatment has been adopted in many institutions as an approach to prevent intraventricular hemorrhage, but there are no strong data to support the practice (33-36). It is stated that the prone position in newborns is more effective than the supine position in providing skin-to-skin contact and oxygenation and ventilation (33). Therefore, in arterial oxygenation, the tidal volume is higher and the $PaCO_2$ is lower. In addition to the prone position, the right lateral position has been shown to be effective in providing oxygenation and ventilation and increasing cerebral oxygenation in the NICU (36). However, sleeping in the prone position is a major risk factor for sudden infant death syndrome. It has been stated that this condition is associated with impaired cerebrovascular control (5). For this reason, it is recommended that parents put newborns to bed in a supine position at home (37).

Scent applications: It is seen that the NIRS device has been used in scent applications that have a positive effect on newborn health in recent years. Changes in cerebral oxygenation in the orbitofrontal cortex are associated with neuronal activation of the olfactory cortex (38,39). During sensory stimulation, there is an increase in oxygen delivery to brain cells. This condition leads to an increase in the concentration of oxygenated hemoglobin in the cerebral cortex (40). Changes in the concentration of oxygenated hemoglobin provide information on oxygen distribution and utilization in connection with cerebral activity (41). There are differences in studies on odor. Cerebral oxygenation levels were found to be higher in newborns who were smelled breast milk than those who smelled formula (40), but smelling breast milk in preterm patients before feeding did not cause a change in cerebral oxygenation (41). While it was found that the smell of hand antiseptic caused fluctuations in cerebral oxygenation in preterms (38), it was reported that the smell of hand antiseptic applied at different waiting periods did not make a difference between the cerebral oxygenation levels of preterms (42).

In music practice: Music is a non-pharmacologic method recommended to reduce stress and pain in preterm newborns hospitalized in NICUs. Music is effective in stabilizing heart and respiratory rates, reducing the frequency of apnea, and improving feeding tolerance (43). Music (such as classical music, lullabies, traditional music, maternal voice) has many benefits in the development of newborns (44). In the literature, the effect of music on cerebral oxygenation levels of newborns is very limited. Different results have been reported: it was observed that hemodynamic changes caused by auditory stimuli in newborns could be reflected by cerebral oxygenation level (45), lullabies and classical music increased cerebral oxygenation in preterms (46), and short-term music therapy had no significant effect on cerebral oxygenation (43).

During sleep: Changes in cerebral oxygenation due to the increase and decrease of neural activity during sleep can be reflected by fluctuations in the brain. However, the number of studies in the literature examining the effect of sleep on cerebral oxygenation levels of newborns is quite limited. NIRS may be helpful in evaluating physiologic and pathologic mechanisms during sleep, investigating cerebral hemodynamic changes that may be caused by sleep disorders such as apnea episodes, and examining the effect of sleep positions on cerebral perfusion (47,48). In studies; decrease in cerebral oxygenation is observed when periodic respiration is performed during active sleep in preterms. Decrease in cerebral oxygenation and increase in fractional oxygen extraction are observed in active sleep in neonates compared to silent sleep. When apnea is experienced during sleep in preterms, a decrease in cerebral oxygenation is observed. It has been reported that there is no significant change in cerebral oxygenation when newborns are given the prone and supine sleeping position in the first postnatal days (47-49). In another study, cerebral oxygenation was found to be low and fractional oxygen extraction was found to be high in the prone sleeping position of unstable extremely preterm newborns. It was stated that this might be a sign of potential brain damage and further studies were needed (49).

Areas Where Abdominal NIRS is Used

In diagnosis, follow-up, treatment, and care planning: It is seen that abdominal NIRS is used in different conditions such as nutritional intolerance, feeding regimens, and NEC (3,10,50). Managing the nutrition of newborns is especially critical for the most vulnerable group, preterm newborns (49). Enteral nutrition is ideal for the development of the gastrointestinal tract in premature neonates due to its

reduction of the risk of nosocomial infections, intestinal motor activity, release of gastrointestinal hormones through trophic effects, and improvement of feeding tolerance (12). However, preterm neonates are at risk for gastrointestinal complications such as feeding intolerance and NEC (7,12). Today, the suspicion of NEC is based on clinical findings and abdominal radiographs are used for diagnosis. However, because the clinical manifestations are not specific to the diagnosis, they can be confused with other pathologic conditions such as sepsis (50). For this reason, NIRS, which has the potential to distinguish other diseases at an early stage, can be used to prevent unnecessary treatment in suspected cases (22). At the same time, it has been stated that enteral feeding increases abdominal oxygenation in stable preterm newborns, splanchnic oxygenation does not change in preterms fed with breast milk, there is a temporary decrease in those fed with enriched breast milk, and a continuous decrease is observed in those fed with formula (39). It has been stated that the frequency of blood transfusions increases the likelihood of developing NEC, abdominal oxygenation increases during and after the procedure, but studies on the effect of nutrition on splanchnic tissue oxygenation during the procedure show variable results (3). Özkan et al. (12), on the other hand, stated that the decrease in mesenteric tissue oxygenation during continuous monitoring of initial enteral nutrition could be used to predict the development of NEC during follow-up. It has been shown that in the presence of hemodynamic ductus arteriosus, there may be a decrease in mesenteric perfusion. Therefore, the limited number of abdominal NIRS studies and the variable results reveal the need to increase research in this area (22).

Evaluation of liver and renal oxygenation: Studies evaluating liver oxygenation are very limited in the literature. Due to the softness of the umbilicus and the change in reflected signals due to peristaltic movements, the instantaneous data of NIRS may give inaccurate results. The hard right upper quadrant can provide more stable signal data than the umbilicus (6,17). When monitoring the oxygenation of the liver, the blood within the vascular network in the liver will also be measured. While liver and sub-umbilical oxygenation was found to be low and fractional tissue oxygenation was found to be high in symptomatic preterm patients with NEC (17), it has been reported that liver oxygenation can be used in the follow-up of mesenteric circulation, but more studies are required. It has been observed that abdominal oxygenation gives very variable results compared with liver oxygenation in stable preterm nutritional intolerance, and although the cerebral oxygenation level remains stable during digestive system operations, the renal oxygenation level tends to decrease (15).

Renal oxygenation monitoring can identify peripheral perfusion changes before they are reflected in pulse oximetry and cerebral oxygenation. Current diagnostic criteria may not detect acute kidney injury at its onset. Therefore, renal oxygenation trends offer a non-invasive approach to the assessment of renal function. It has been observed that renal NIRS can provide data on hypoxic states in the intraoperative and postoperative period, and the use of ibuprofen in preterm patients with patent ductus arteriosus (PDA) does not adversely affect renal and mesenteric oxygenation (6,26).

In olfactory applications: Sensory cues from smell can trigger physiologic responses that facilitate the digestion and metabolism of food (38,39). The smell of breast milk in tube-fed preterms may contribute to an increase in the sucking reflex, acceleration of the transition to oral feeding, an increase in abdominal perfusion, and a decrease in hospital stay. At the same time, positive odor stimulation provides intestinal motility, insulin secretion, release of metabolic hormones, and increased appetite (39). Studies evaluating the effect of scent applications on abdominal oxygenation are very limited.

Differences in Cerebral and Abdominal Oxygenation Assessment

In term newborns, oxygen distribution to vital organs such as the brain should be ensured during labor. Therefore, renal and intestinal oxygenation in stable term neonates may be lower compared with cerebral oxygenation. In stable preterm neonates, cerebral oxygenation values remain mostly constant, whereas renal and mesenteric measurements usually fluctuate considerably because the abdominal region is more sensitive than the cerebral region and is affected by the movements and bowel movements of the newborn (15). For this reason, cerebral oxygen extraction may be higher than mesenteric oxygen extraction in preterm patients with respiratory problems in the postpartum transition period, and an increase in both may be observed over time. Thus, cerebral and mesenteric oxygen extraction may be affected by physiologic changes with gestational week and postnatal age, and normal ranges of cerebral and mesenteric oxygen saturation remain uncertain in extremely low birth weight preterm neonates, especially through postnatal day 7 (5,6,43).

It has been determined that the abdominal oxygenation value of stable preterm newborns in the first weeks of life is lower in those with a lower gestational age (15), and that the changes in cerebral and mesenteric tissue oxygenation of stable very low birth weight babies of >30 days postnatally do not show a significant difference. Studies have emphasized that this may also be due to the clinical stability of infants and the difference between their postnatal ages. Depending on the clinical status of preterm newborns, a significant increase in abdominal tissue oxygen saturation can be detected compared with cerebral tissue oxygen saturation after blood transfusion, or there may be a positive correlation between hemoglobin concentrations and cerebral and abdominal oxygenation (10,15). In their

systematic review, Crispin and Forwood (48) examined the role of NIRS in the cerebral, splanchnic, renal, and muscle regions to detect anemia and guide transfusion decisions, and found that there was a correlation between hemoglobin concentrations and tissue oxygenation. However, it has been stated that more research is needed on the values of tissue oxygenation, which may lead to negative clinical outcomes. It has been shown that post-transfusion cerebral oxygen saturation is increased in preterm neonates with and without PDA, whereas splanchnic oxygenation is lower before, during, and after transfusion in those with PDA. Measurement of cerebral oxygenation in preterm and term neonates has older and clearer evidence than measurement of bowel, kidney, and liver oxygenation.

Reflections of NIRS on the Nursing Profession and Its Use in Neonatal Care

NICUs are areas where newborns are monitored with medical and surgical problems and continuous nursing care and invasive interventions are applied. It is very important for health professionals to adopt a multidisciplinary approach to evaluate critical situations and manage the treatment process effectively (25). This includes the coordinated work of the neonatal physician and the neonatal intensive care nurse in NIRS follow-up. Nurses should diagnose newborns at an early stage in terms of risks that may cause various mortality and morbidity and should perform careful follow-up. One of the guiding devices in this regard is NIRS, which provides ease of use due to its ability to be used at the bedside and is a non-invasive procedure (2). It can be used effectively in many nursing care applications such as the evaluation of vital signs, positioning, intravenous applications, nutritional applications such as orogastric catheter sets, aspiration applications, tracheostomy care, and diaper changing (5).

The fact that preterm babies feel pain frequently and that it persists for a long time may cause neurologic complications in the future. During painful procedures, practices such as kangaroo care, swaddling, and position changes relieve pain and provide changes in cerebral oxygenation levels (25). Therefore, one of the aims of nursing care practices applied to intensive care patients is to protect and maintain tissue oxygenation. For this reason, the points that nurses should pay attention to in monitoring the NIRS device, which is becoming more common in newborns, are important. Thus, the effective use of NIRS devices by nurses plays an important role in protecting newborns from secondary problems (2).

There are some points that nurses should pay attention to in the placement, replacement times, follow-up, and evaluation of NIRS probes:

- The neonatal nurse should position the NIRS sensor according to the area to be evaluated, then attach the end of the sensor cable to the module parts on the monitor and make sure that it fits snugly. Otherwise, the signal quality will be poor and the NIRS value will not be readable (50).
- Placing the sensor on fat deposits, hair, bone spurs, nevi, hematomas, edema or cracked skin, or applying pressure to the sensor may result in inaccurate readings. Nurses should be careful and not stick the probe in these areas (50).
- In newborns receiving phototherapy treatment, the light of the phototherapy device may affect the NIRS value. To avoid this situation, it is recommended to cover the sensor with dark material. The nurse needs to regularly monitor the position of the NIRS probe with phototherapy goggles (50).
- If NIRS monitoring is used in conjunction with electroencephalography, care should be taken to ensure that the area where the probe is attached is clean, as the materials used to attach the electrodes can affect the signal quality.
- Since the adhesive tapes used for umbilical catheter detection in abdominal NIRS follow-up may affect the signal quality, attention should be paid to the place where the probe is attached, and the area should be cleaned (10).
- NIRS values are affected by the baby's movements, improper positioning of the sensor, gestational age, mode of delivery, and the type of device used. There are different emitters, wavelengths, and algorithms among the devices used, and different oxygenation values can be measured (4,16,26).
- It is important for nurses to pay attention to the change of probe location, as prolonged insertion of the NIRS probe in the same spot can lead to inaccurate measurements and irritation (15). In NIRS monitoring studies, skin burns, pressure sores, and persistent skin irritations at term have been observed, especially in preterm neonates (3). Although there is no conclusive evidence of replacement time, it is recommended that nurses change the probe location every 4-6 hours, judging by skin irritation and the need to reposition the sensor. In preterm neonates, the change period may be more frequent according to need. At the same time, the sensor should be replaced every 24 hours. It has been shown that reapplying sensors used in the same area in 24 INVOS devices can lead to a degree of inaccuracy of up to 6% (26).
- It is reported that skin burns that may occur due to the use of transcutaneous NIRS in newborns are not caused by damage to the tissue by light intensities, but are a result of the sensor being stuck in the same point for a long time, especially due to the skin sensitivity of extremely preterm newborns (6).

- Major weight changes in the first weeks of life can affect the depth reading of the NIRS sensor. In a study evaluating cerebral, renal, and intestinal oxygenation, a weak positive correlation was found between weight change in the first weeks of life and only intestinal oxygenation in preterm newborns (15).
- After the NIRS probe is attached, it is necessary to wait for a certain period for net measurement. Abnormal values in the first minutes should not be taken into account by the nurse (7,17). Due to the inherent variability of the measurements performed with NIRS sensors, it is important to monitor the baseline data for a sufficient period (several hours) for an accurate result. NIRS values tend to change with increasing postnatal age and can be influenced by factors such as anemia, hypotension, and acidosis (2,15). Nurses should not ignore these conditions in regional tissue oxygenation follow-up.
- Although cerebral oxygenation values remain mostly constant in stable preterm neonates, there are large fluctuations in renal and mesenteric measurements. The purpose of NIRS measurements is to observe persistent and/or frequent changes that are greater than 15% from baseline (2,15). Hyperoxia and hypoxia are undesirable conditions for newborns. Therefore, the tissue oxygenation index reference range of newborns is expected to be between 55% and 85%. In particular, a NIRS value below 45% is considered a dangerous area and the nurse must inform the physician (16). In this respect, it is critical for nurses to have sufficient knowledge of NIRS values for follow-up and evaluation.
- A NIRS value below 55% may occur in conditions such as hypocarbia, hypotension, PDA, anemia, and low arterial saturation, and above 85% may occur in conditions such as hypercarbia, supranormal arterial saturation and hypoglycemia (16). The neonatal nurse should keep in mind that oxygen is a drug and should consider hyperoxia and hypoxia in the evaluation of regional oxygenation.
- Probes may be irritated, frayed, and ruptured due to long use. In such cases, nurses need to replace the probe with a new one.
- A probe is often attached under the umbilicus to evaluate abdominal oxygenation. Especially if intestinal oxygenation is to be evaluated, the bottom of the umbilicus is preferred due to the wide size of the neonatal abdomen and the confounding effect of the current position of the renal and hepatic tissues (7,15). The sub-umbilicus bladder and pelvic wall may also reflect the oxygenation of muscle tissue, but it is thought to affect it less than the major organs (6). In addition, abdominal oxygenation is difficult to evaluate due to the inside, hollow structure of the intestine, peristalsis, and large surface area (2). Nurses should consider these factors when following up infants undergoing abdominal oxygenation monitoring.

Conclusion

In recent years, the measurement of oxygen consumption of tissues using NIRS technology has become increasingly common in neonatal centers. NIRS can be used effectively in many nursing practices such as the evaluation of vital signs, non-pharmacologic interventions, intravenous applications, aspiration applications, and tracheostomy care. It is seen that the use of NIRS in Türkiye is mostly research-based and its use in the clinic is very limited. The increasing number of studies is promising for its widespread use in the clinic. There is no review in the literature that deals with the nursing care dimension of NIRS use. It is thought that nurses' knowledge of the points they need to pay attention to regarding the use of NIRS and their reflection on their care will contribute to the use of the device in nursing care. With the expansion of work in this area and the increasing spread of this technology in neonatal units, the tool can be used in the routine care of newborns in the near future. In addition, it is important to increase research by considering the diversity in NIRS devices and probes, the high cost of the device, the fact that it is affected by many factors such as gestational week, and the difficulties in interpreting regional oxygenation, such as deficiencies in universal normative values.

In the literature, it is seen that there are more studies on preterm newborns for NIRS technology compared with term neonates. At the same time, studies on the effects of smell, music, sleep and position on cerebral and abdominal oxygenation seem to be limited. In studies on diagnosis, treatment, and care, there are variable results. For this reason, it is recommended to increase medical and nursing studies and clinical awareness in preterm and term newborns. In conclusion, the measurement of cerebral oxygenation in preterm and term neonates has older and clearer evidence than the measurement of gut, kidney, and liver oxygenation. However, for the use of NIRS to become a standard monitoring technique, studies need to be expanded and increased.

Footnotes

Authorship Contributions

Concept: H.Ö., S.Y., Design: H.Ö., S.Y., Data Collection or Processing: H.Ö., S.Y., Analysis or Interpretation: H.Ö., S.Y., Literature Search: H.Ö., S.Y., Writing: H.Ö., S.Y.

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