

MEDICAL RECORDS

International Medical Journal

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Kisspeptin-54 Ameliorates Electrocardiographic Abnormalities in an Experimental Parkinson's Rat Model

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Abstract

Aim: Cardiac complications may arise in association with Parkinson's disease as age progresses. Kisspeptins are a group of peptides that mediate their physiological functions by binding to the GPR54 receptor. This study aimed to investigate whether KP-54 has an effect on the electrical activity of the heart in an animal model of Parkinson's disease.

Material and Method: Sprague-Dawley rats weighing between 290–310 g were used. An experimental hemiparkinsonian rat model was generated via stereotaxic injection of the neurotoxin 6-OHDA into the right medial forebrain bundle, effectively replicating unilateral dopaminergic neuronal loss. Rats received either control (aCSF, 5 µL, ICV) or KP-54 (3 nmol/kg, ICV) treatment once daily for seven consecutive days. At the end of the seventh day, behavioral tests were conducted on the rats. Following the behavioral tests, electrocardiographic (ECG) recordings were obtained.

Results: 6-OHDA significantly increased catalepsy time ($p<0.001$), which was effectively reduced by KP-54 ($p<0.05$). In the open field test (OFT), rats injected with 6-OHDA showed decreased distance traveled ($p<0.001$) and velocity ($p<0.01$) compared to controls, whereas KP-54 treatment partially improved these motor impairments ($p<0.01$). ECG data revealed that the heart rate (HR), impaired following 6-OHDA administration ($p<0.01$), returned to control levels in the 6-OHDA + KP-54 group ($p<0.01$). There were no notable differences between the groups regarding P duration, PR and QRS interval. However, the QT and QTc intervals were significantly increased ($p<0.01$) in the Parkinson's group and were normalized to control levels in the 6-OHDA + KP-54 group ($p<0.05$). These findings indicate that KP-54 corrected the QT prolongation induced by 6-OHDA.

Conclusion: In conclusion, the present findings suggest that alterations in HR and prolongation of the QT interval observed in Parkinson's disease could be prevented by the neuropeptide kisspeptin. Nevertheless, further research involving different administration routes is required to validate and expand upon these results.

Keywords: Electrocardiography, Kisspeptins, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopamine-producing neurons in the substantia nigra. This neuronal loss leads to the development of motor symptoms, including tremors, rigidity, and bradykinesia (1,2). While current treatments (e.g., levodopa and dopamine agonists) alleviate symptoms, they do not halt disease progression and may cause side effects, including cardiovascular issues (3). Autonomic dysfunction, such as orthostatic hypotension and arrhythmias, is common and can be worsened by dopaminergic therapy, underscoring the

need for treatments targeting both neurological and cardiovascular aspects of PD (4).

Kisspeptins are neuropeptides central to reproductive hormone regulation via activation of GnRH neurons in the hypothalamus (5). Encoded by the KISS1 gene, they are processed into active forms like kisspeptin-54 (KP-54), KP-14, KP-13, and KP-10, all acting through the GPR54 (KISS1R) receptor (6). KP-54 stands out for its longer half-life (~32 minutes vs. ~4 minutes for KP-10) and ability to cross the blood-brain barrier, allowing for more sustained central effects compared to shorter, rapidly cleared fragments (7).

Emerging evidence indicates that kisspeptins have significant effects beyond the reproductive axis, including

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roles in the cardiovascular system. GPR54 is expressed in cardiovascular tissues such as blood vessels and the heart (8). In the cardiovascular system, it is found in endothelial cells and cardiomyocytes, suggesting a direct role in modulating vascular tone, heart rhythm, and contractility (9). While its precise effects are still being studied, current evidence points to involvement in vasoconstriction and blood pressure regulation. Studies show that KP-10, KP-13, and KP-54 act as potent vasoconstrictors, similar to angiotensin II, and KP-10 enhances cardiac contractility in rodents and humans (9,10). These effects suggest kisspeptin modulates vascular tone, heart rate, and myocardial function. Notably, KP-54 can cross the blood-brain barrier, potentially influencing central cardiovascular regulation (7). While these findings highlight its therapeutic potential, further research is needed to clarify kisspeptin's role in cardiovascular physiology and disease.

PD patients often experience autonomic and cardiac issues, raising the question of whether kisspeptin affects cardiac function in this context. While kisspeptin's effects on blood pressure and heart rate have been studied, its influence on cardiac electrophysiology remains largely unknown, with no direct data on ECG parameters. Therefore, the present study was designed to investigate the effects of KP-54 on electrocardiographic parameters in a hemiparkinsonian rat model. We utilized 6-hydroxydopamine (6-OHDA) to create an experimental PD model and evaluated whether central administration of KP-54 could ameliorate ECG abnormalities. In particular, we focused on how KP-54 influences heart rate and various ECG intervals (P wave, PR, QRS, QT, and corrected QT) in 6-OHDA-lesioned rats. By addressing this gap, our study aims to shed light on the potential cardio-regulatory effects of KP-54 in a PD context.

MATERIAL AND METHOD

Animals

Adult male Sprague-Dawley rats (weighing 290–310 g) were used for all experiments. Rats were housed in transparent Plexiglas cages in a temperature-controlled room ($22 \pm 2^\circ\text{C}$) with a 12-hour light/dark cycle. They had free access to standard chow and water ad libitum. All experimental procedures were conducted in accordance with institutional and international guidelines for animal care and were approved by the Akdeniz University Faculty of Medicine Animal Ethics Committee (Approval No. 1689/2024.04.002, Decision date: 15.04.2024). Throughout the study, efforts were made to minimize animal stress and discomfort.

Experimental Design

In the hemiparkinsonian rat model, 6-OHDA, a catecholaminergic neurotoxin, was administered into the right medial forebrain bundle using stereotaxic injection. The rats were administered either a vehicle (control) treatment or KP-54 (intracerebroventricular, ICV) once daily for seven consecutive days. The control treatment consisted of an injection of artificial cerebrospinal fluid

(5 μL , ICV). The final dose of KP-54 was administered to the rats on the seventh day, 30 minutes before conducting the behavioral tests. Electrocardiographic (ECG) recordings were obtained one hour after the behavioral tests. Motor function in the 6-OHDA-induced PD model was objectively evaluated through the open field and catalepsy tests. Detailed experimental procedures are outlined in Figure 1.

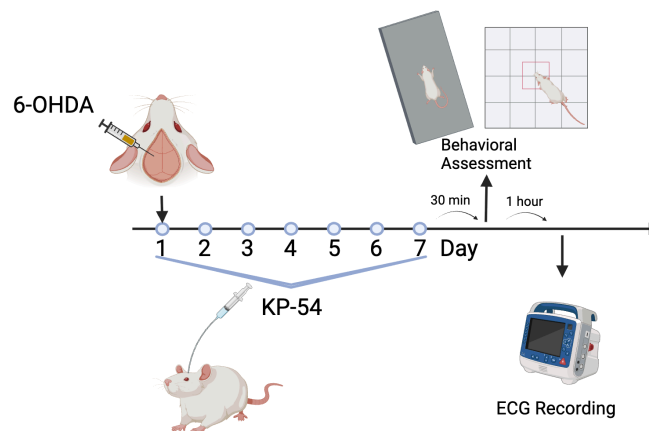


Figure 1. An overview of the experimental procedure timeline

Surgery

Following intraperitoneal administration of ketamine (60 mg/kg) and xylazine (12 mg/kg), the animals were placed in a stereotaxic apparatus. The 6-OHDA (3 $\times$ 4 $\mu\text{g}/\mu\text{L}$) was injected stereotactically into the right medial forebrain bundle using the following coordinates: 2.2 mm anteroposterior, 1.5 mm mediolateral (ml), and 8 mm dorsoventral relative to the bregma. The 6-OHDA solution prepared fresh in sterile saline with 0.2 mg/ml ascorbic acid, was administered in a 3 μL volume. In the sham surgery group, 0.1% ascorbic acid was used as a vehicle control. The syringe was kept in place for an additional 3 minutes to allow for optimal diffusion of the neurotoxin. To administer KP-54 (3 nmol/kg) via the ICV route, a cannula was surgically inserted into the lateral ventricle (11). After lesion induction, a 26G polyethylene cannula was placed stereotactically into the right lateral ventricle using coordinates of 0.8 mm AP, 1.4 mm ML, and 4 mm DV from the bregma and skull surface, based on a rat brain atlas. To maintain stability, the cannula was firmly fixed in place using screws and dental cement. Central KP-54 ICV injections were administered every day for seven days.

ECG Recordings

Electrocardiographic recordings were obtained on the final day of the experiment to evaluate cardiac electrical activity in each group. One hour after completion of the behavioral tests on the 7th day, rats were re-anesthetized with a light dose of ketamine (50 mg/kg i.p.) and xylazine (5 mg/kg i.p.) to minimize movement while preserving autonomic function as much as possible. Once anesthetized, each rat was placed in a supine position, and standard lead II ECG electrodes

were attached (subdermal needle electrodes). The ECG was continuously recorded for a period of 10 minutes using the data acquisition system (Biopac Systems, Inc., USA) at a sampling rate of 1 kHz. During recording, body temperature was maintained with a warming pad, and the depth of anesthesia was monitored to ensure the absence of pain reflexes while maintaining a relatively stable heart rate. The following ECG parameters were measured from the lead II recordings: heart rate (HR, beats per minute), P wave duration, PR interval, QRS complex duration, QT interval, and corrected QT (QTc) interval. Heart rate was determined by counting the number of R-wave peaks over the 10-minute recording period (and expressed as bpm). The QT interval was measured from the start of the QRS complex to the end of the T wave; QTc was calculated using Bazett's formula ($QTc = QT / \sqrt{RR \text{ interval}}$) (12). For each rat, multiple cardiac cycles were analyzed to obtain representative values for intervals. ECG traces were analyzed offline using LabChart software (ADInstruments, NZ) by an investigator blinded to group assignments. Any ECG segments with movement artifacts were excluded from the analysis.

Statistical Analysis

All data were analyzed using GraphPad Prism 8.0 (GraphPad Software, USA). Prior to statistical comparisons, datasets were checked for normality using the Shapiro-Wilk test. For normally distributed data, group comparisons were performed using one-way analysis of variance (ANOVA). This was followed by Tukey's post hoc test for multiple comparisons to identify differences between specific groups. Behavioral outcomes (catalepsy duration, open field distance, and velocity) and ECG parameters (HR, intervals) were each analyzed with one-way ANOVA across the three groups (Control, 6-OHDA, 6-OHDA+KP-54). All results are reported as the mean $\pm$ standard error of the mean (SEM). A threshold of $p < 0.05$ was considered statistically significant. In figures, statistically significant differences are indicated with asterisks or other annotations as described in the figure legends.

RESULTS

KP-54 Reduces the Motor Deficits Caused by 6-OHDA

In comparison to the control rats (1.24 ± 0.09 s, $n=7$), 6-OHDA exhibited a marked increase in catalepsy duration (2.55 ± 0.28 s, $p < 0.001$, $n=7$). The elevation in catalepsy time induced by 6-OHDA was reduced by KP-54 (1.87 ± 0.15 s, $p < 0.05$, $n=7$), suggesting that KP-54 effectively mitigated the cataleptic effects of 6-OHDA (Figure 2A).

In the OFT, control rats traveled a typical distance. The 6-OHDA group (1982 ± 175.9 cm, $n=7$) displayed a notable decrease in locomotor activity compared to the control rats (975.7 ± 123.7 cm, $p < 0.001$, $n=7$). On the other hand, the 6-OHDA + KP-54 group (1703 ± 119.8 cm, $p < 0.01$, $n=7$) showed a partial recovery in locomotor function (Figure 2B).

The control group (7.43 ± 0.44 cm/s, $n=7$) exhibited the highest average velocity during the test. However, the 6-OHDA group (3.48 ± 0.37 cm/s, $p < 0.001$, $n=7$) showed a significant reduction in velocity, emphasizing the detrimental impact of 6-OHDA on movement velocity. Notably, administration of KP-54 (5.64 ± 0.41 cm/s, $p < 0.01$, $n=7$) led to a significant improvement in mean velocity, indicating a partial but meaningful recovery (Figure 2C).

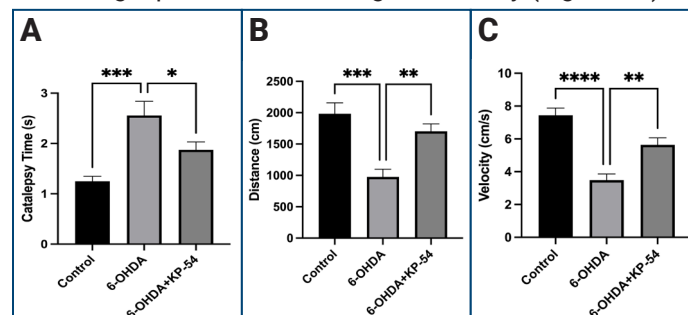


Figure 2. The impact of KP-54 administration on motor performance parameters (catalepsy duration, **A**; total distance traveled, **B**; and velocity, **C**) was evaluated in a hemiparkinsonian rat model. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test ($n=7$ rats per group); Levels of significance are indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; All data are presented as mean $\pm$ S.E.M

As demonstrated in our previous study, the findings indicate that 6-OHDA causes motor impairments, evidenced by prolonged catalepsy duration and reductions in both distance traveled and movement speed (11). In contrast, ICV central administration of KP-54 helps reduce these motor impairments induced by 6-OHDA.

KP-54 Restored the Increased QTc Interval to Its Baseline Following 6-OHDA Administration

Figure 3 illustrates the electrocardiographic parameters (including HR, P duration, QRS complex duration, PR, QT interval, and QTc) measured after 6-OHDA and KP-54 administration. HR refers to the number of heartbeats occurring within a 10-minute time period. In the group treated with 6-OHDA (250.7 ± 8.03 bpm, $n=7$), heart rate (HR) was significantly reduced when compared to the control rats (293.3 ± 7.41 bpm, $p < 0.01$, $n=7$). This reduction was reversed to control levels following KP-54 administration (296.8 ± 6.39 bpm, $p < 0.01$, $n=7$, Figure 3A). The P wave duration, PR interval, and QRS duration did not exhibit any significant changes in either the 6-OHDA group or the 6-OHDA + KP-54 group (Figure 3B-C-D).

However, when examining the QT interval and QTc duration, a notable elevation was detected in the 6-OHDA group (71.44 ± 3.24 ms and 159.6 ± 12.53 ms, $p < 0.01$, $p < 0.05$, respectively; $n=7$) compared to the control rats (56.86 ± 3.22 ms and 114.9 ± 2.98 ms, respectively; $n=7$). In contrast, in the 6-OHDA + KP-54 group (58.4 ± 1.8 ms and 111.2 ± 2.92 ms, $p < 0.05$, $p < 0.05$, respectively; $n=7$), these values returned to control levels (Figure 3E-F).

The data show that in the 6-OHDA-induced hemiparkinsonian rat model, only the QT interval was significantly prolonged in the ECG waves, and this prolongation was reversed after the administration of KP-54.

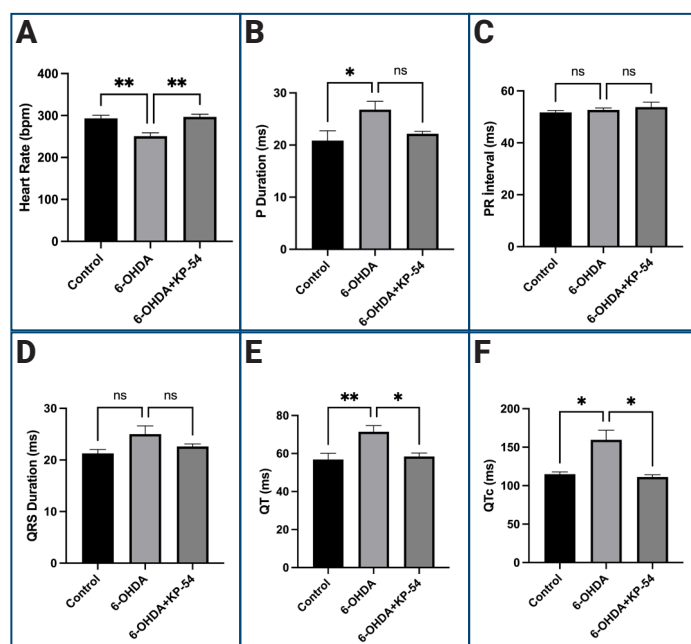


Figure 3. Electrocardiographic assessment of rats administered with 6-OHDA and 6-OHDA+KP-54; Each bar represents the alterations observed in ECG parameters; Statistical comparisons of group means were conducted using one-way ANOVA followed by Dunnett's test; Statistical significance levels are represented as follows: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$; All data are presented as mean $\pm$ S.E.M; All values are expressed as the mean $\pm$ S.E.M

DISCUSSION

In this study, we investigated the effects of the neuropeptide KP-54 on cardiac electrical abnormalities in a rat model of PD. Our major findings can be summarized as the 6-OHDA lesion resulted in marked ECG changes, including a reduced heart rate and prolonged QT/QTc intervals relative to control groups. This suggests that the PD model produced bradycardia and a delay in cardiac repolarization, which are reminiscent of autonomic dysfunction-related cardiac effects. Notably, the KP-54 treatment normalized the heart rate and brought the abnormally prolonged QT and QTc intervals back to the control level. To our knowledge, this is the first direct evidence that KP-54 can modulate ECG parameters in an experimental Parkinsonian setting. The findings raise the possibility that kisspeptins have beneficial effects on the autonomic and cardiovascular dysfunction associated with PD.

The relationship between kisspeptin and PD is a novel area of investigation. However, our research team findings and other emerging evidence suggest that kisspeptin signaling may favorably influence PD-related pathology. One potential link is through neuroprotection: PD is characterized by the loss of specific neuronal populations (e.g., dopaminergic neurons and also some cholinergic and other brainstem neurons). Recent studies indicate that kisspeptin might have neuroprotective properties (11,13). Another aspect of the kisspeptin-PD relationship is the modulation of motor and mood circuits (14). Although kisspeptin has not traditionally been associated with CVS in the context of PD, our findings, together with supporting studies, suggest that kisspeptin may have a significant impact on PD symptoms

(11, 13-15). In this regard, it emerges as a promising target for advancing our understanding of PD pathophysiology and developing novel therapeutic strategies.

In our study, a hemiparkinsonian model was induced using 6-OHDA, followed by a seven-day treatment with KP-54. Due to the lack of existing literature on the ICV administration of KP-54 in a rat model, our previous study established a dose-response curve based on motor performance outcomes and identified 3 nmol/kg as the effective dose, which was consistently administered over a period of seven days (11). The ICV route was selected for the administration of KP-54 to ensure effective delivery to brain regions associated with cardiovascular regulation, as oral or intravenous routes may reduce efficacy and such compounds often face challenges in crossing the blood-brain barrier.

Cardiovascular system involvement is a common but sometimes underappreciated aspect of PD. A substantial body of clinical evidence indicates that autonomic nervous system (ANS) dysfunction is a frequent non-motor feature of PD (16). Cardiovascular autonomic dysfunction can manifest as orthostatic hypotension, resting bradycardia, altered blood pressure variability, and even cardiac arrhythmias in PD patients (3). Epidemiological studies suggest that roughly 80% of PD patients have some form of cardiovascular abnormality related to autonomic failure (17).

In the context of cardiac electrophysiology, autonomic impairment in PD often leads to measurable ECG changes. One well-documented finding is a reduction in heart rate variability (HRV) in individuals with PD. HRV reflects the balance of sympathetic and parasympathetic inputs to the heart, and PD patients typically manifest reduced beat-to-beat variability, indicative of diminished parasympathetic (vagal) tone to the heart (18).

Given these autonomic changes, not surprisingly, various ECG abnormalities have been reported in PD patients. Beyond HRV changes, PD patients can exhibit subtle prolongation of conduction intervals or repolarization (19). Our findings suggest that as PD progresses, the cardiac conduction system may be increasingly affected (through autonomic or direct cardiac involvement). The QT interval and its heart-rate-corrected form (QTc) have also drawn attention in PD (18-21). Prolongation of the QT/QTc can predispose individuals to ventricular arrhythmias (like Torsades de Pointes), thus it is clinically relevant. Studies have noted that a significant subset of PD patients have an abnormally prolonged QTc. According to Malkiewicz et al. (2021), between 16% and 21% of PD patients in their study exhibited prolonged QTc intervals and they suggested that PD itself—regardless of medication use—could be a contributing risk factor (20). Older age and male sex were also associated with longer QTc in PD, and the authors could not exclude a specific predilection of PD for QTc prolongation. They recommended vigilant cardiac monitoring in PD patients, especially those on medications that affect QTc (20). Our 6-OHDA-lesioned rats showed QTc

prolongation (relative to controls), which is consistent with the notion that parkinsonian pathology (even in an animal model) can lead to repolarization changes. It is worth noting that the QTc prolongation in PD could stem from intrinsic cardiac sympathetic denervation (leading to electrical remodeling) or from side effects of PD drugs (many PD medications, such as some antidepressants used for PD depression or even domperidone used for nausea, can lengthen QT). In our experiment, drugs were not a confounding factor, so the QTc prolongation is more likely related to the 6-OHDA's effects on the autonomic network controlling the heart.

A key question arising from our work is whether kisspeptin's effects on heart rate and ECG are mediated centrally (via the brain) or peripherally (directly on the heart). Our experimental design, which used ICV KP-54, inherently targets central receptors first. The fact that KP-54 crossed out of the ventricular system to peripheral circulation is likely but not certain, however, given the small peptide size and one-hour gap between injection and ECG recording, some peripheral spillover is plausible. To tease apart the mechanism, one can consider prior studies: In healthy humans, intravenous infusion of KP-54 did not produce significant changes in heart rate or blood pressure (22). This implies that in a physiologically normal state, activating peripheral GPR54 (or even central GPR54 via a peptide that might reach the brain partially) has minimal effect on cardiovascular parameters.

In contrast, significant changes were observed following central administration of KP-54 in rats included in our PD model, suggesting that central effects may be the primary determinant. The peptide likely exerted its effects by modulating the already impaired autonomic network. In a study by Nijher et al., KP-54 was shown to have no effect on blood pressure or heart rate in healthy individuals (23). Considering this, KP-54 administration in healthy rats would not be expected to induce changes in the QT interval (note: in our study, a Control+KP-54 group was not established). Peripheral GPR54 activation is known to increase cardiac contractility (24). However, the study by Nijher et al. demonstrated that KP-54 had no impact on blood pressure or heart rate, indicating that its effects do not arise through peripheral pathways. However, our findings suggest that heart rate and QTc values may be similar between control rats and lesion-induced rats receiving KP-54. This finding supports the existence of a central compensatory mechanism: KP-54 likely exerted its effect only in the lesioned group, where an imbalance existed, thereby restoring homeostasis, while inducing no significant changes in the already balanced control group (23).

CONCLUSION

In conclusion, our study lays the groundwork by showing that KP-54 has multi-faceted benefits in an experimental PD scenario. The findings encourage further research

into kisspeptin's mechanisms and its potential as a novel therapeutic avenue. If future studies confirm these benefits in more chronic and translational models, kisspeptin or kisspeptin-based drugs could become a part of the repertoire to treat PD – not only addressing the classic motor symptoms but also the critical autonomic and cardiac manifestations that impact patient safety and quality of life.

Limitation

While our study provides important new data on the role of KP-54 in a PD model, several limitations should be acknowledged.

First, the 6-OHDA hemiparkinsonian model is a convenient and well-established platform for motor studies, but the autonomic effects of 6-OHDA lesions are relatively mild and acute. In idiopathic PD, cardiac sympathetic denervation and vagal impairment develop over years. Thus, it will be important to test whether KP-54 has similar beneficial effects in models that more closely mimic chronic PD, for example, an α -synuclein overexpression model or environmental toxin model that develops cardiac autonomic dysfunction over time.

Second, our ECG recordings were performed under anesthesia, which could influence the results. Anesthesia (especially the combination of ketamine/xylazine we used) tends to depress heart rate and alter autonomic tone. Although all groups were under the same anesthetic protocol, and we waited a standardized period before recording, the absolute heart rate values are on the low side for rats (even our control rats were ~293 bpm, whereas awake rats often have heart rates above 350 bpm). The anesthesia might have blunted the differences between groups or introduced its own effects on QT interval.

Third, we did not directly measure any autonomic or molecular endpoints to pinpoint mechanism. We infer mechanism from outcomes and existing literature. It would strengthen the conclusions to measure, for instance, plasma catecholamine levels, or tissue norepinephrine content in the heart, to see if KP-54 restored sympathetic neurotransmitter levels in 6-OHDA rats.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: All experimental procedures were conducted in accordance with institutional and international guidelines for animal care and were approved by the Akdeniz University Faculty of Medicine Animal Ethics Committee (Approval No. 1689/2024.04.002, Decision date: 15.04.2024).

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The Impact of Wearable Technology on Median Nerve Conduction Studies: A Comparative Analysis of Smartwatch and Traditional Watch Wearers

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Abstract

Aim: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, presenting with pain, numbness, and tingling in the hands. Factors such as occupational and lifestyle habits, repetitive movements, and external compression contribute to its development. This study aims to evaluate the relationship between continuous daily smartwatch use and median nerve electrophysiological features, comparing it with traditional watch users.

Material and Method: A total of 96 adult participants were included, comprising individuals who did not use any type of watch and those who had used either a smartwatch or a traditional watch for at least three months. Data on demographics, watch use habits, and Boston Carpal Tunnel Syndrome Questionnaire scores were collected. We performed median nerve conduction studies (NCS) and evaluated the combined sensory index (CSI) values.

Results: Ninety-six participants were enrolled: 35 without watches, 29 using traditional watches, and 32 using smartwatches. Smartwatch users demonstrated non-significant but more frequent and prolonged daily usage compared to traditional watch users ($p>0.05$). No significant differences were observed in NCS findings across the three groups ($p>0.05$). While 13.5% of participants showed median sensory NCS results compatible with CTS, this proportion increased to 41.4% when $CSI>1.0$ ms used as a criterion. The CSIs were similar in all three groups ($p=0.79$). No significant differences were found when comparing the frequency of $CSI>1.0$ ms between watch-wearing and non-wearing sides for both traditional watches (24.1% vs. 31.0%, $p=0.77$) and smartwatch users (25.0% vs. 18.8%; $p=0.76$).

Conclusion: To the best of our knowledge, our study is the first to systematically investigate the effect of smartwatch use on median nerve electrophysiological findings. Our findings suggest frequent occurrences of asymptomatic CTS-related electrophysiological changes. However, these changes were not associated with significant differences in symptoms or NCS findings among smartwatch or traditional watch users.

Keywords: Carpal tunnel syndrome, nerve conduction studies, wearable technology, median nerve, smartwatch

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most prevalent focal mononeuropathy, affecting approximately 7–18.4% of the general population (1-3). Symptoms include pain, paresthesia, and, less commonly, muscle weakness in the hands (4,5). Various factors contribute to its pathophysiology, including occupational and lifestyle habits, repetitive wrist movements, and external compression (4,5).

CTS is typically diagnosed through clinical symptoms such as pain, tingling, and paresthesia in the radial 3½ digits, corresponding to the median nerve distribution (5,6). Elevated interstitial pressure within the carpal tunnel leads

to sub-synovial fibrosis, median nerve demyelination, and eventual axonal degeneration (4). Management options range from preventive strategies to medical or surgical treatments, guided by electrophysiological evaluations (4,5).

Electrodiagnostic tests like nerve conduction studies (NCS) and electromyography (EMG) are pivotal in assessing the extent of median nerve damage. These tests can reveal impaired nerve conduction, prolonged latencies, and axonal degeneration (7). This study investigates the potential impact of daily smartwatch use on CTS development, comparing findings with traditional watch users and individuals not wearing watches.

CITATION

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MATERIAL AND METHOD

The study was approved by the Karabük University Clinical Research Ethics Committee and conducted in accordance with the Declaration of Helsinki (Date: 01/06/2022, Decision No: 2022/934). Informed consents were obtained from all participants. The methodology was summarized in the flowchart (Figure 1).

We included three groups of volunteers prospectively in the study: volunteers aged 18 or older who had used smartwatches or traditional watches for at least three months or who had not worn any watches or bracelets in the last six months. Exclusion criteria comprised rheumatologic, neurologic, or cardiac conditions, hypothyroidism, diabetes, upper extremity or cervical spinal surgeries, polyneuropathy, trauma, deformity, or cognitive impairment.

A total of 96 participants were included: 35 without watches, 29 traditional watch users, and 32 smartwatch users. Demographic data included age, sex, height, weight, occupation, educational level, hand dominance, and watch use habits (type, duration, frequency) were recorded.

The Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), created by Lavine and colleagues (8), was used as a scoring system in this study. The BCTQ evaluates symptom severity (11 items) and functional capacity (8 items), with scores ranging from 1 (mild) to 5 (severe). The total score of the symptom severity scale and functional status scale of the questionnaires were used in this study. The visual analog scale (VAS) score is used to assess the pain level of patients.

NCS were performed using the Keypoint® Focus EMG/ NCS/EP system. The median and ulnar nerve sensory NCS and radial nerve sensory NCS were performed on all participants. Sensory NCS were conducted antidromically, with recordings taken from ring electrodes. For the median nerve, the sensory distal latency upper limit was set at 3.40 ms for the 14 cm segment from the second finger to the wrist, and the lower limit for sensory conduction velocity was set at 49 m/s. Motor NCS were performed by stimulating the wrist (8 cm) and elbow. The potentials were recorded with surface disc electrodes from the abductor pollicis brevis. For the median nerve, the upper limit for motor distal latency was set at 4 ms, and the lower limit for conduction velocity was set at 50 m/s. Additionally, median mixed sensory NCS were performed including median-ulnar mixed sensory NCS for the 8 cm segment from fourth finger to wrist, median-ulnar palmar mixed sensory NCS for the 8 cm segment from palm to wrist, and median-radial mixed sensory NCS for the 10-12 cm segment from first finger to wrist. CTS was diagnosed if there was a slowing of sensory conduction velocity, prolonged sensory distal latency, and/or prolonged motor distal latency (9). We have calculated the combined sensory index (CSI) previously described by Lew et al., and CSI>1.0 ms is considered significant for CTS (10).

We compared the NCS of both upper extremities of not-watch users with those of the watch-wearing upper extremity in participants using a traditional or smartwatch. Additionally, comparisons were made between the watch-wearing and non-wearing extremities of participants using watches.

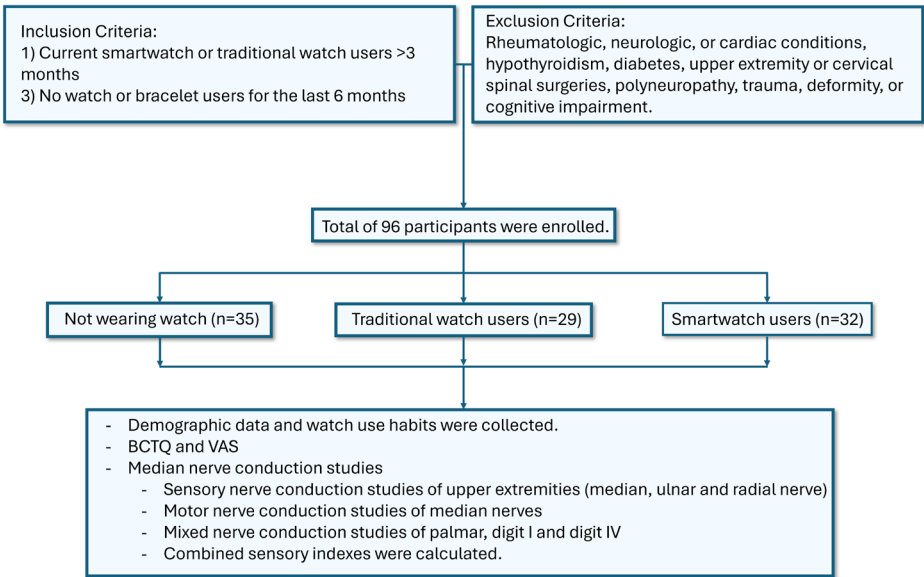


Figure 1. The flow diagram of the study

Statistical Analysis

Shapiro-Wilk tests and histograms were used to assess data normality. Categorical variables were compared using Fisher’s exact test, and continuous variables using Mann-Whitney U or Kruskal-Wallis tests. Binomial

logistic regression analysis was used to evaluate factors influencing CSI>1.0 ms. Multicollinearity was evaluated with tolerance and variance inflation factors. Statistical significance was set at p<0.05 and analyses were performed using Jamovi (v2.3.28).

RESULTS

A total of 96 participants were included: 35 without watches (24 female, 11 male), 29 traditional watch users (15 female, 14 male), and 32 smartwatch users (18 female, 14 male). Demographic and clinical characteristics are summarized in Table 1. Age, gender, height, weight, and body mass index (BMI) were comparable across the groups, though participants not wearing watches tended to be older, predominantly female, and exhibited higher BMI values. Most participants were right-handed (83% in non-watch users, 97% in both traditional and smartwatch users; $p=0.08$). A majority of watch wearers used their left wrist (83% in traditional watch users, 81% in smartwatch users; $p=1$).

Traditional watch users reported significantly longer cumulative wear duration (Table 1, $p<0.01$). While smartwatch users tended to use their watches more regularly and for longer periods daily, these differences were not statistically significant ($p=0.46$ and $p=0.15$, respectively). VAS pain scores and BCTQ symptom severity and functional status scores were similar across groups.

The sensory and motor median nerve NCS results did not differ significantly among the groups (Table 2, Figure 2). Combined sensory index (CSI) values were slightly higher in non-watch users, though not statistically significant ($p=0.79$). Mild CTS, diagnosed based on sensory latency and conduction velocity of the median nerve at digit II, was observed in four participants (11.4%) without watches, five traditional watch users (17.2%), and four smartwatch users (12.5%).

When considering $CSI>1.0$ ms as a criterion, 41.7% of all participants exhibited values suggestive of CTS. This

included 41.3% of traditional watch users and 28.1% of smartwatch users ($p=0.30$). No significant differences were found when comparing the frequency of $CSI>1.0$ ms between watch-wearing and non-wearing sides for both traditional watches (24.1% vs. 31.0%, $p=0.77$) and smartwatch users (25.0% vs. 18.8%; $p=0.76$).

Within the traditional watch group, no significant differences in NCS findings were observed between watch-wearing and non-wearing extremities. The CSI was slightly higher on the non-wearing side, but this difference was not statistically significant ($p=0.37$; Table 3).

In smartwatch users, significant differences were noted between the wearing and non-wearing sides in terms of median sensory NCS latency and amplitude recorded at digit II, ulnar palmar latency, and median-ulnar palmar mixed NCS (Table 4). However, all findings were within normal limits and lacked clinical significance. Additionally, the difference in CSI between sides was not statistically significant ($p=0.84$).

Binomial logistic regression analysis assessed factors influencing $CSI>1.0$ ms. The model was statistically significant ($\chi^2(9)=21.3$, $p=0.01$) and accounted for 28.8% of the variance in the outcome (Nagelkerke $R^2=0.288$). No multicollinearity was observed among the included factors.

BMI was significantly associated with higher odds of $CSI>1.0$ ms (OR=1.25, 95% CI: 1.07–1.47, $p<0.01$). Other variables, including BCTQ scores, age, cumulative watch-wearing duration, daily watch-wearing time, and type of watch (traditional or smartwatch), did not show significant associations with $CSI>1.0$ ms.

Table 1. Demographic and clinical characteristics of the participants				
	Not wearing watch (N=35)	Traditional watch users (N=29)	Smartwatch users (N=32)	p-value
Age, median (IQR)	37.0 (24.0-45.0)	30.0 (22.0-42.7)	29.5 (25.0-33.6)	0.14*
Gender, female (%)	24/35 (69%)	15/29 (41%)	18/32 (56%)	0.09**
Height (cm), median (IQR)	165 (159-175)	173 (160-176)	170 (163-183)	0.10*
Weight (kg), median (IQR)	69 (58-78)	70 (58-80)	70 (60-81)	0.81*
Body-mass index	24.6 (21.2-26.5)	23.1 (20.4-27.8)	23.2 (21.8-26.2)	0.67*
Hand preference, right	29/35 (83%)	24/25 (97%)	31/32 (97%)	0.08**
The side of the watch, left	NA	24/29 (83%)	26/32 (81%)	1**
Total wearing time, median months (IQR)	NA	60 (44-84)	24 (12-36)	<0.01***
Wearing time, days in a week	0.46**			
3-4	NA	5/29 (17%)	3/32 (9%)	
5-7	NA	24/29 (83%)	29/32 (91%)	
Wearing time, hours in a day	0.15**			
0-6	NA	2/29 (7%)	3/32 (9%)	
6-12	NA	13/29 (45%)	10/32 (31%)	
12-18	NA	11/29 (35%)	8/32 (25%)	
18-24	NA	3/29 (10%)	11/32 (34%)	
Wearing during sleep	NA	13/29 (45%)	11/32 (34%)	0.44**
VAS, median (IQR)	0 (0-1)	0 (0-1)	0 (0-0)	0.90*
BCTQ-SSS, median (IQR)	11 (11-15)	11 (11-12)	12 (11-16)	0.14*
BCTQ-FSS, median (IQR)	8 (8-10)	8 (8-8)	8 (8-12)	0.48*
IQR: interquartile range, VAS: visual analog scale, BCTQ-SSS: Boston carpal tunnel syndrome questionnaire-symptom severity scale, BCTQ-FSS: Boston carpal tunnel syndrome questionnaire-functional status scale; *Kruskal-Wallis test, **Chi-square test, ***Mann-Whitney U test				

Table 2. Comparison of nerve conduction study results

	Not wearing watch (N=70)*	Traditional watch users (N=29)*	Smartwatch users (N=32)*	p-value**
Sensory nerve conduction studies				
Median nerve				
Digit I (latency, ms)	2.3 (0.3)	2.3 (0.4)	2.3 (0.2)	0.84
Digit II (latency, ms)	2.9 (0.3)	2.9 (0.5)	2.9 (0.4)	0.90
Digit II (amplitude, μ V)	29.2 (10.3)	27.5 (14.1)	30.4 (8.7)	0.54
Digit II (conduction velocity m/s)	63.4 (5.5)	62.8 (7.1)	63.3 (5.1)	0.56
Digit IV (latency, ms)	2.8 (0.3)	2.8 (0.6)	2.9 (0.4)	0.76
Palmar (latency, ms)	1.6 (0.3)	1.6 (0.3)	1.6 (0.3)	0.85
Ulnar nerve				
Digit IV (latency, ms)	2.7 (0.3)	2.8 (0.5)	2.8 (0.5)	0.32
Palmar (latency, ms)	1.1 (0.4)	1.2 (0.5)	1.0 (0.2)	0.57
Radial nerve				
Digit I (latency, ms)	2.1 (0.4)	2.0 (0.7)	2.2 (0.6)	0.24
Motor nerve conduction studies				
Median nerve				
Digit II (latency, ms)	2.7 (0.4)	2.6 (0.4)	2.8 (0.4)	0.09
Digit II (amplitude, mV)	7.6 (2.4)	8.2 (1.8)	8.1 (2.3)	0.08
Digit II (conduction velocity, m/s)	58.4 (5.7)	57.1 (6.3)	57.4 (4.8)	0.38
Mixed nerve conduction studies				
Digit IV (median-ulnar) difference, ms	0.1 (0.2)	0.0 (0.2)	0.0 (0.2)	0.15
Digit I (median-radial) difference, ms	0.3 (0.5)	0.2 (0.6)	0.0 (0.6)	0.11
Palmar (median-ulnar) difference, ms	0.5 (0.5)	0.4 (0.6)	0.5 (0.3)	0.30
Combined sensory index	0.78 (0.9)	0.64 (0.7)	0.64 (0.8)	0.79

Electrophysiological findings of both upper extremities in participants not wearing a watch were compared with those of the watch-wearing upper extremity in participants using a traditional or smartwatch

*Median (interquartile range), **Kruskal Wallis test was used

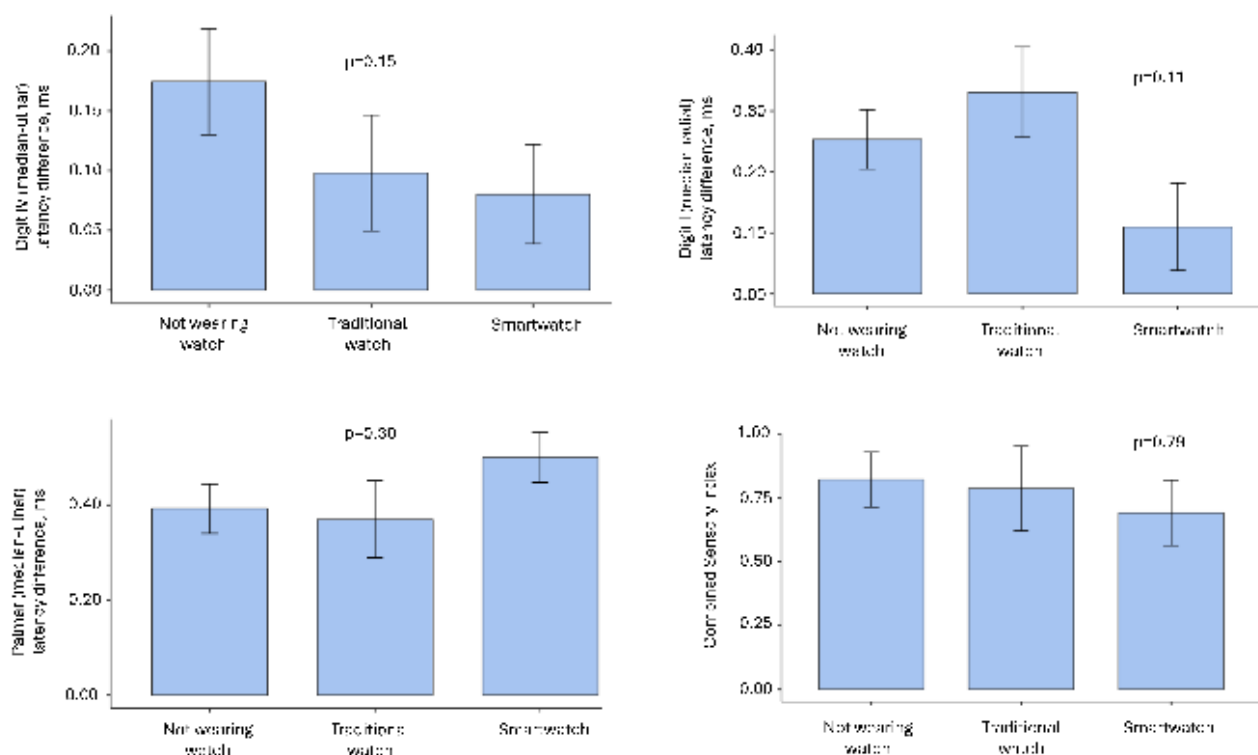


Figure 2. Mixed nerve conduction studies revealed no significant latency differences of median-ulnar nerve on digit IV, median-radial nerve on digit I and median-ulnar nerve on palmar studies between the groups ($p=0.15$, $p=0.11$, $p=0.30$, respectively); The combined sensory indexes were similar in all groups ($p=0.79$); Values are presented as mean $\pm$ standard error of the mean

Table 3. Comparison of nerve conduction studies and combined sensory indexes between the traditional watch-wearing side and the non-traditional watch-wearing side

N=29	Traditional watch-wearing side*	Non-traditional watch-wearing side*	p-value**
Sensory nerve conduction studies			
Median sensory nerve			
Digit I (latency, ms)	2.3 (0.4)	2.3 (0.4)	0.17
Digit II (latency, ms)	2.9 (0.5)	2.9 (0.7)	0.06
Digit II (amplitude, μ v)	27.5 (14.1)	26.2 (9.9)	0.35
Digit II (conduction velocity m/s)	62.8 (7.1)	59.6 (8.8)	0.49
Digit IV (latency, ms)	2.8 (0.6)	2.8 (0.6)	0.78
Palmar (latency, ms)	1.6 (0.3)	1.6 (0.4)	0.31
Ulnar nerve			
Digit IV (latency, ms)	2.8 (0.5)	2.8 (0.4)	0.17
Palmar (latency, ms)	1.2 (0.5)	1.0 (0.5)	0.15
Radial nerve			
Digit I (latency, ms)	2.0 (0.7)	2.0 (0.5)	0.97
Motor nerve conduction studies			
Median motor nerve			
Digit II (latency, ms)	2.6 (0.4)	2.7 (0.6)	0.76
Digit II (amplitude, mv)	8.2 (1.8)	8.7 (2.2)	0.90
Digit II (conduction velocity, m/s)	57.1 (6.3)	57.3 (4.7)	0.52
Mixed nerve conduction studies			
Digit IV (median-ulnar) difference, ms	0.0 (0.2)	0.0 (0.2)	0.55
Digit I (median-radial) difference, ms	0.2 (0.6)	0.4 (0.5)	0.74
Palmar (median-ulnar) difference, ms	0.4 (0.6)	0.6 (0.6)	0.12
Combined sensory index, ms	0.64 (0.7)	0.79 (0.6)	0.37

*Median (Interquartile range), **Wilcoxon signed-rank test was used

Table 4. Comparison of nerve conduction studies and combined sensory indexes between the smartwatch-wearing side and the non-smartwatch-wearing side

N=32	Smartwatch-Wearing Side*	Non-Smartwatch-Wearing Side*	p-value**
Sensory nerve conduction studies			
Median sensory nerve			
Digit I (latency, ms)	2.3 (0.2)	2.4 (0.2)	0.26
Digit II (latency, ms)	2.9 (0.4)	2.9 (0.3)	0.02
Digit II (amplitude, μ v)	30.4 (8.7)	28.3 (9.9)	0.05
Digit II (conduction velocity m/s)	63.3 (5.1)	63.1 (7.2)	0.90
Digit IV (latency, ms)	2.9 (0.4)	2.9 (0.3)	0.29
Palmar (latency, ms)	1.6 (0.3)	1.6 (0.2)	0.85
Ulnar nerve			
Digit IV (latency, ms)	2.8 (0.5)	2.7 (0.4)	0.42
Palmar (latency, ms)	1.0 (0.2)	1.2 (0.2)	0.02
Radial nerve			
Digit I (latency, ms)	2.2 (0.6)	2.2 (0.6)	0.54
Motor nerve conduction studies			
Median motor nerve			
Digit II (latency, ms)	2.8 (0.4)	2.7 (0.5)	0.53
Digit II (amplitude, mv)	8.1 (2.3)	8.1 (2.3)	0.24
Digit II (conduction velocity, m/s)	57.4 (4.8)	58.7 (5.0)	0.84
Mixed nerve conduction studies			
Digit IV (median-ulnar) difference, ms	0.0 (0.2)	0.1 (0.2)	0.17
Digit I (median-radial) difference, ms	0.0 (0.6)	0.0 (0.6)	0.86
Palmar (median-ulnar) difference, ms	0.5 (0.3)	0.4 (0.3)	0.04
Combined sensory index, ms	0.54 (0.8)	0.58 (0.7)	0.84

*Median (Interquartile range), **Wilcoxon signed-rank test was used

DISCUSSION

The CTS is the most common peripheral neuropathy, significantly affecting patients' functionality. It is primarily idiopathic, with female sex and increased age identified as key risk factors (2,5). Mechanical factors such as forceful gripping and repetitive wrist movements further contribute to its development by increasing carpal tunnel pressure (11). Pressure is predicted to increase tenfold with wrist extension but only eightfold with flexion (12). Other risk factors include but are not limited to rheumatological diseases, pregnancy, hypothyroidism, menopause, obesity, and amyloidosis (5,13). The underlying pathophysiology involves elevated pressure within the carpal tunnel and ischemia-induced axonal degeneration of the median nerve, manifesting as clinical symptoms (12).

Wearable technologies such as smartwatches are increasingly integrated into daily life, offering benefits like tracking vital signs, heart rhythm, and sleep quality. As a result, smartwatches may be worn for longer periods compared to traditional watches, potentially affecting carpal tunnel pressure—a key factor in CTS development (12).

Wearable devices utilize photoplethysmography to measure parameters like oxygen saturation and heart rate. This involves emitting green, red, or infrared light, which penetrates tissue to varying depths; infrared light can reach up to 5 cm (14). Although infrared radiation may have beneficial effects, its potential for heat generation and the impact of long-term exposure on peripheral nerves remain unclear (15). Additionally, LED light sources and tighter straps may increase skin temperature, potentially affecting nerve conduction. Studies have shown that temperature increases can reduce sensory amplitude in CTS patients, likely due to heat-induced conduction blocks (16). Therefore, in case of CTS, using smartwatches may alter median nerve electrophysiology. The literature search revealed only one case series in the literature has linked smartwatch use to CTS symptoms, which improved after discontinuation (17).

In our study, we extensively evaluated the median nerve in participants using traditional watches, smartwatches, or no watches at all. Demographic and clinical characteristics were similar across groups, with no differences in BCTQ scores or VAS pain scores. This finding is consistent with the fact that none of the participants had a prior diagnosis of CTS. There was no difference in the NCS findings of all three groups in any NCS (Table 2). Based on the median sensory NCS on digit II, 11.4% to 17.2% of participants in different groups were diagnosed with CTS. In population-based studies, the frequency of CTS was found between 7% to 18.4% similar to our results (1,2). However, extensive NCS in our study showed that an increased CSI (>1.0 ms) rate may be up to 41.7%.

The CSI were similar in all groups with a slight tendency of increase in the group of participants not wearing a watch

($p=0.79$). The slightly higher CSI observed in participants who do not wear watches may be explained by their higher BMI, advanced age, and female predominance (18). Logistic regression analysis further supported BMI as the only significant predictor of increased CSI (OR=1.25, 95% CI: 1.07–1.47, $p<0.01$).

In our study, smartwatch users wear them more often during the week and longer times during the day which may increase the pressure within the carpal tunnel and compress the median nerve. Conversely, traditional watch users have a longer total wearing time which may cause continuous compression for a longer time ($p<0.01$). Although traditional watch users reported longer cumulative wear times compared to smartwatch users, this did not translate into differences in CSI, suggesting that duration and pressure dynamics may be less critical than other factors such as BMI or individual anatomy ($p>0.05$).

When comparing NCS results between the watch-wearing and non-wearing sides, no significant differences were noted in traditional watch users ($p=0.37$). A slight trend toward increased CSI on the non-wearing side could be attributed to the preference for wearing watches on the non-dominant hand. Among smartwatch users, statistically significant differences were found in median sensory NCS on digit II as well as ulnar palmar latency and median-ulnar palmar latency difference (Table 4). However, all measurements remained within normal limits, and these differences did not affect CSI values ($p=0.84$).

Several limitations should be acknowledged. The small sample size and single-center design may limit the generalizability of our findings. Additionally, as a cross-sectional study, it cannot capture participants who may develop CTS over time. Furthermore, the study lacked reliable data on strap tightness, which could influence compression levels and alter NCS results. Prospective longitudinal studies in larger, diverse populations are warranted to address these gaps.

CONCLUSION

This study examined the effects of daily smartwatch use on median NCS. To the best of our knowledge, this is the first research attempt to systematically investigate the relation between smartwatch use and median nerve electrophysiological features. Although CTS prevalence was consistent with population-based estimates, elevated CSI values were observed across all groups. Despite this, smartwatch and traditional watch use did not result in significant differences in CTS symptoms or NCS findings.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: This study was approved by the Karabük University Clinical Research Ethics Committee (Date: 01/06/2022, Decision No: 2022/934).

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Anticonvulsant and Neuroprotective Effects of Felodipine in a PTZ-Induced Epileptic Seizure Model

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Abstract

Aim: This research sought to evaluate the anticonvulsant properties of Felodipine in a rat model of pentylenetetrazol (PTZ)-induced seizures, with a particular focus on its modulatory effects on neuroinflammatory responses and oxidative stress biomarkers.

Material and Method: The entirety of 48 male Wistar rats were separated into two main groups for behavioral and electrophysiological assessments. The anticonvulsant properties of Felodipine at dosages of 10 mg/kg and 20 mg/kg were evaluated according to seizure severity, using Racine's Convulsion Scale and the latency to the First Myoclonic Jerk (FMJ). Electroencephalographic (EEG) recordings were analyzed to measure epileptiform activity by assessing the proportion of spike-wave discharges. Neuroinflammatory and oxidative stress markers, namely tumor necrosis factor-alpha (TNF- α) and malondialdehyde (MDA), were quantified in brain tissue using Enzyme-linked immunosorbent assay (ELISA) and Thiobarbituric Acid Reactive Substances (TBARS) tests, respectively. A p-value of less than 0.05 was deemed statistically significant.

Results: Felodipine significantly decreased seizure intensity and prolonged FMJ start time relative to the PTZ and saline-treated cohorts ($p < 0.05$). EEG recordings revealed a marked decrease in spike percentages in the Felodipine-treated groups. Furthermore, biochemical analyses demonstrated that Felodipine significantly reduced TNF- α and MDA levels, indicating its neuroprotective effects by mitigating neuroinflammation and oxidative stress.

Conclusion: The PTZ-induced seizure model showed that felodipine significantly reduced seizure activity, neuroinflammation, and oxidative stress, indicating robust anticonvulsant and neuroprotective benefits. Its favorable safety profile and dual-action mechanism targeting calcium channels and inflammatory pathways position it as a promising candidate for epilepsy management. Further studies are warranted to explore its long-term efficacy and potential in chronic epilepsy models.

Keywords: Epilepsy, felodipine, calcium channel blockers, neuroinflammation, oxidative stress, anticonvulsant therapy

INTRODUCTION

Recurrent and spontaneous seizures are the hallmarks of epilepsy, a chronic neurological illness affecting over 50 million people globally. The necessity for new treatment options is underscored by the fact that, despite the availability of numerous antiepileptic medicines (AEDs), over 30 % of patients have drug-resistant epilepsy (1,2). This unmet medical need has encouraged the exploration of alternative approaches with novel mechanisms and the repurposing of existing drugs for different indications.

In this context, calcium channel blockers (CCBs) have emerged as promising candidates for the treatment of epilepsy. Neuronal excitability, synaptic transmission, and intracellular signaling are all significantly impacted by L-type voltage-gated calcium channels (VGCCs),

which CCBs aim to block. Felodipine, a dihydropyridine CCB widely used in the treatment of hypertension, has demonstrated anticonvulsant potential in several preclinical studies (3-5). Its ability to modulate calcium influx and reduce excitatory neurotransmission provides dual benefits in seizure control and neuroprotection.

Calcium ions play a central role in neuronal physiology, including action potential generation, neurotransmitter release, and intracellular signaling cascades. However, excessive calcium influx through VGCCs, particularly L-type channels, contributes significantly to the pathophysiology of epilepsy. Prolonged calcium entry triggers excitotoxicity, leading to neuronal damage and hyperexcitability, which contribute to the initiation and propagation of seizures (6,7). Felodipine's action on

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these channels reduces intracellular calcium levels, alleviating these pathological processes and stabilizing hyperexcitable neural networks.

The efficacy of felodipine as an antihypertensive agent is attributed to its high vascular selectivity and potent inhibition of L-type calcium channels in smooth muscle. This property minimizes systemic side effects and makes it a suitable candidate for repurposing in neurological conditions. Preclinical studies have shown that felodipine exhibits significant anticonvulsant effects in PTZ- and maximal electroshock (MES)-induced seizure models (2,5,6). These effects are thought to result from its ability to increase seizure thresholds, reduce seizure severity, and mitigate neuroinflammation and oxidative stress.

For example, studies have shown that felodipine reduces the duration and frequency of seizures in rodent models, with minimal sedative effects. The neuroprotective advantages of this compound are further shown by its ability to reduce inflammatory markers like TNF- α and oxidative stress indicators like MDA (4,6,7).

Additionally, nimodipine and diltiazem, two additional calcium channel blockers, have been studied for their anticonvulsant effects. For instance, nimodipine has been found effective in reducing seizure severity in animal models; however, dose-dependent cardiovascular side effects limit its clinical application (3,5,6). Felodipine's higher vascular selectivity and lipophilicity allow it to cross the blood-brain barrier more effectively and reduce peripheral side effects (7,8).

The pathophysiology of epilepsy is influenced by neuroinflammation and oxidative stress, according to recent studies. In the epileptic brain, proinflammatory cytokines like TNF- α and interleukin-1 β are increased, which worsens neuronal hyperexcitability and aids in the advancement of the condition. Likewise, oxidative stress caused by the overproduction of reactive oxygen species (ROS) results in lipid peroxidation, protein oxidation, and DNA damage, which further diminishes neuronal function (6,7). Felodipine's ability to mitigate these processes adds a neuroprotective dimension to its anticonvulsant effects. By reducing TNF- α levels and MDA concentrations, it not only controls seizure activity but also prevents secondary neuronal damage, positioning it as a promising candidate for long-term epilepsy management (7,8).

The mechanisms underlying the anticonvulsant and neuroprotective effects of felodipine remain insufficiently explored despite promising preclinical evidence. Most studies have focused on its impact on seizure activity, with limited data on its role in modulating neuroinflammatory and oxidative stress pathways.

The purpose of this research is to fill these knowledge gaps by studying felodipine's impact on a model of PTZ-induced seizures. Specifically, it investigates the drug's impact on seizure severity, onset latency, and biochemical

markers of neuroinflammation and oxidative stress. By integrating behavioral, electrophysiological, and biochemical analyses, this research seeks to provide a comprehensive understanding of felodipine's therapeutic potential in the treatment of epilepsy.

MATERIAL AND METHOD

Animal and Laboratory

The research process for this work received approval from the Animal Ethics Board of Science University (Approval Number: 0123113305). Following the guidelines set forth by the National Institutes of Health (U.S.), all procedures involving the use of laboratory animals were carried out.

The research used 48 male Wistar rats, each weighed between 200 and 250 grams. Of these, 24 rats were allocated for EEG recordings, whilst the other 24 were earmarked for behavioral evaluations. A peaceful habitat with an ambient temperature of 22-24°C was provided for the animals, and they were maintained on a 12-hour light-dark cycle (lights on from 07:00 to 19:00). All participants were allowed unlimited access to tap water and standard laboratory diet.

Methods for Conducting Experiments

Forty-eight rats were randomly assigned to one of two groups: Group A, which was used to record the EEG, and Group B, which was used for behavioral assessment. Group A rats were stereotactically drilled with a small hole in their heads after a powerful anesthetic was administered to them. The left frontal cortex dura mater was implanted with stainless steel electrodes that were covered with polyamide. The electrodes had a diameter of 0.1 mm and an electrical resistance of less than 1 Ω /10 mm. The midline reference electrode was positioned 1.5 mm behind the lambda on the cerebellum (9). Dental acrylic, a material often used in tooth restoration procedures, was employed to attach the electrodes. Ketamine (80 mg/kg) and xylazine (4 mg/kg) were administered intraperitoneally to begin anesthesia.

The PTZ dosage of 35 mg/kg was used, as previously applied in our earlier study, since it reliably creates identifiable EEG spike activity without consistently eliciting obvious behavioral alterations, while 70 mg/kg results in significant behavioral changes but compromises the EEG signal-to-noise ratio for dose-dependent studies (10). Twelve days post-electrode implantation, the 24 rats in Group A were randomly allocated into four subgroups (n=6 each): A1, A2, A3, and A4.

- **Group A1 (Control):** No therapy provided,
- **Group A2 (Saline):** Rats were administered saline intraperitoneally,
- **Group A3 (Felodipine 10 mg/kg):** Rats received an intraperitoneal injection of 10 mg/kg Felodipine,
- **Group A4 (Felodipine 20 mg/kg):** Rats received an intraperitoneal administration of 20 mg/kg Felodipine.

Felodipine doses of 10 mg/kg and 20 mg/kg were selected based on previous studies demonstrating their efficacy in seizure models (3,4). All pharmacological interventions were administered 30 minutes prior to PTZ administration (35 mg/kg, intraperitoneally). EEG recordings were performed five minutes post-PTZ treatment in conscious rats situated in a dedicated enclosure.

The EEG signals were captured for 60 minutes using the BIOPAC MP150 Data Acquisition System (Biopac Systems Inc., Santa Barbara, CA, USA), amplified by a factor of 10,000, and filtered within a frequency range of 1–60 Hz. The spike percentage, indicative of epileptiform activity, was measured as the ratio of 1-second periods containing at least one spike-wave event ("spike-wave percentage") (10). This measurement was evaluated by two clinical neurophysiologists. The initiation and cessation of spike-wave complexes were determined by amplitudes exceeding twice the baseline values. Cumulative spike-wave lengths were assessed at 2-minute intervals.

In Group B, a distinct cohort of 24 rats was randomly allocated into four subgroups (n=6 each): B1, B2, B3, and B4.

- **Group B1 (Control):** No therapy provided,
- **Group B2 (Saline):** Rats were administered saline by intraperitoneal injection,
- **Group B3 (Felodipine 10 mg/kg):** Rats received an intraperitoneal administration of 10 mg/kg Felodipine,
- **Group B4 (Felodipine 20 mg/kg):** Rats received an intraperitoneal administration of 20 mg/kg Felodipine.

Pharmacological interventions were delivered 30 minutes before to the PTZ administration (70 mg/kg, intraperitoneally). Using the latency to the "FMJ" and Racine's Convulsion Scale (RCS) seizures were assessed (10). The severity of the seizures was assessed as follows, and the FMJ latency was measured in seconds:

0=Absence of seizure,

1=Twitching of vibrissae and pinnae,

2=Motor arrest accompanied by significant twitching,

3=Generalized myoclonic jerks (FMJ onset time documented),

4=Tonic-clonic seizure with preserved posture,

5=Tonic-clonic seizure with loss of righting reflex,

6=Fatal seizure.

There was a 30-minute restriction on the observation duration for PTZ-induced seizures. Following anesthesia (100 mg/kg ketamine, Richterpharma AG, Austria, and 50 mg/kg xylazine, Bayer, Germany), all rats were cervically dislocated and put to death at the end of the trial. The brains were subsequently taken for biochemical assessments and further tests.

Assessment of Cerebral Lipid Peroxidation

Malondialdehyde (MDA) levels were measured using the thiobarbituric acid reactive substances (TBARS) technique to evaluate lipid peroxidation as described before (11). Samples were treated with trichloroacetic acid and TBARS reagent, followed by mixing and incubation at 100°C for 60 minutes. Following refrigeration on ice, the samples were subjected to centrifugation at 3000 rpm for a duration of 20 minutes. The absorbance of the supernatant was measured at 535 nm. MDA concentrations were quantified using a standard calibration curve utilizing tetraethoxypropane and expressed as nmol/g protein.

Quantification of Cerebral Protein Concentrations

Total protein concentrations in brain homogenates were measured using the Bradford assay, following the method described before (12). Bovine serum albumin was used as the standard in the Bradford test to measure the amount of total protein in brain samples.

Examination of Brain TNF- α

Upon extraction, brain tissues were promptly preserved at -20°C for biochemical examination. Using a glass homogenizer, the brain tissues were mixed in five liters of phosphate-buffered saline (PBS, pH 7.4) for tissue preparation. They were then centrifuged for 15 minutes at 5000 g. After collecting the supernatant, the Bradford test was used to measure the amount of protein present in the brain homogenate overall.

The levels of tumor necrosis factor- α in the brain tissue supernatants were assessed using ELISA kits that are commercially available for rats. Following the instructions provided by the manufacturer (eBioscience, Inc, San Diego, CA), each sample was examined twice. A MultiscanGo microplate reader (Thermo Fisher Scientific, NH, USA) was used to measure absorbance.

Statistical Evaluation

Every outcome is shown as the mean plus or minus the standard error of the mean (SEM). We used SPSS 15.0 for Windows to conduct the statistical analyses. We used the Shapiro-Wilk test to make sure the data was normally distributed. The FMJ delay was analyzed using a one-way analysis of variance (ANOVA), whereas Racine's convulsion scores were analyzed using the Kruskal-Wallis test. Mann-Whitney U tests and post hoc Bonferroni analyses were used to compare the two experimental groups. We regarded $p < 0.05$ as having statistical significance.

RESULTS

This research thoroughly assessed the impact of Felodipine on the PTZ-induced seizure model by behavioral, electrophysiological, and biochemical metrics. The findings are detailed below.

1. Behavioral Assessments

Convulsion Stage (Racine Scale)

We used the Racine Convulsion Scale to measure the impact of Felodipine on seizure severity. While the control group (Stage 0) showed no seizure activity, the PTZ and saline-treated group (Group 2) had an average convulsion stage of 5.4±0.5 (Table 1). However, the convulsion stage significantly decreased to 3.6±0.2 (*p<0.05) in the group treated with 10 mg/kg Felodipine (Group 3). In the group receiving 20 mg/kg Felodipine (Group 4), this value was further reduced to 2.8±0.5 (**p<0.001). These results

demonstrate that Felodipine effectively reduces seizure severity.

Onset Time of the First Myoclonic Jerk (FMJ)

The FMJ onset time of 68.2±7.7 seconds was recorded in the group that was treated with PTZ and saline. The duration was notably extended to 105.4±12.3 seconds (*p<0.05) in the cohort administered 10 mg/kg Felodipine compared with 162.1±16.5 seconds (**p<0.001) in the cohort receiving 20 mg/kg Felodipine (Table 1). The data demonstrate that Felodipine postpones seizure onset, underscoring its anticonvulsant properties.

Table 1. Behavioral assessments: Convulsion stage and FMJ onset time		
Groups	Convulsion stage (Racine)	FMJ onset time (sec)
1-Control	0	0
2-PTZ (70 mg/kg) and saline	5.4±0.5	68.2±7.7
3-PTZ (70 mg/kg) and 10 mg/kg felodipine	3.6±0.2*	105.4±12.3*
4-PTZ (70 mg/kg) and 20 mg/kg felodipine	2.8±0.5**	162.1±16.5**
Data were expressed as mean±SEM; Statistical analyses were performed by one-way ANOVA test; *p<0.05, ** p<0.001 (different from saline-treated PTZ group)		

2. Electrophysiological Assessments

EEG Spike Activity

The electrical activity of seizures was evaluated through EEG recordings, and spike percentages were calculated (Table 2). The control group had no spike activity, but the PTZ plus saline-treated group demonstrated a spike percentage of 73.6±8.3. Treatment with 10 mg/kg Felodipine resulted in a considerable reduction in the spike % to 55.2±10.6 (**p<0.01), while administration of 20 mg/kg Felodipine further lowered it to 41.8±9.1 (**p<0.01). Examples of EEG recordings are shown in Figure 1. Figure 1A shows a normal EEG pattern in the control group without PTZ or Felodipine administration. In contrast, Figure 1B illustrates pronounced epileptiform spikes in the PTZ (35 mg/kg) and saline group. Figure 1C and Figure 1D demonstrate a noticeable reduction in spike activity in the groups treated with 10 mg/kg and 20 mg/kg of Felodipine, respectively, indicating its dose-dependent protective effect.

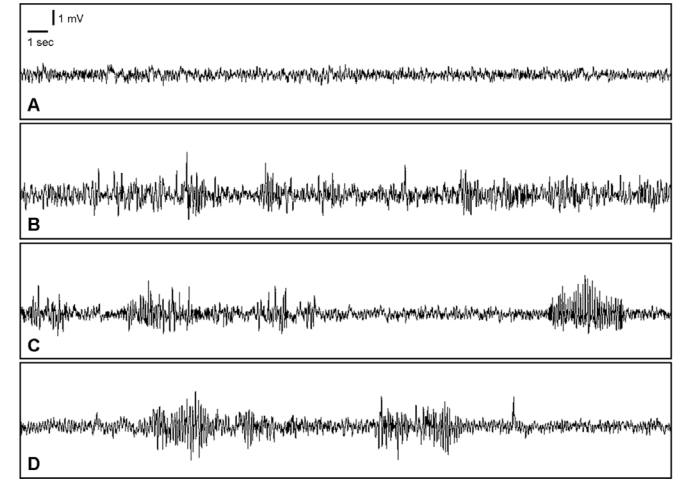


Figure 1. Representative EEG recordings: (A) Control Group; (B) PTZ (35 mg/kg) and saline group; (C) PTZ (35 mg/kg) and 10 mg/kg Felodipine group; (D) PTZ (35 mg/kg) and 20 mg/kg Felodipine group

Table 2. EEG spike activity	
Groups	Spike percentage
1-Control	0
2-PTZ (70 mg/kg) and saline	73.6±8.3*
3-PTZ (70 mg/kg) and 10 mg/kg felodipine	55.2±10.6**
4-PTZ (70 mg/kg) and 20 mg/kg felodipine	41.8±9.1**
Data were expressed as mean±SEM; Statistical analyses were performed by one-way ANOVA test; *p<0.05, **p<0.01 (different from saline-treated PTZ group)	

3. Biochemical Assessments

Lipid Peroxidation Indicator (MDA)

Malondialdehyde (MDA) levels were measured to assess Felodipine's impact on oxidative stress (Table 3). There was a substantial rise in MDA levels to 23.7±3.02 nmol/g protein in the PTZ and saline-treated groups (*p<0.05). In contrast, the MDA levels decreased to 11.2±1.6 nmol/g protein (#p<0.05) in the group treated with 10 mg/kg Felodipine and to 9.5±0.8 nmol/g protein (##p<0.01) in the group treated with 20 mg/kg Felodipine. These findings demonstrate that Felodipine reduces oxidative stress markers.

Neuroinflammation Indicator (TNF-α)

Levels of TNF-α were assessed to determine the anti-inflammatory capabilities of Felodipine (Table 3). In the PTZ and saline-treated group, TNF-α levels were measured at 133.4±7.5 pg/mg protein (**p<0.001). TNF-α levels

dramatically dropped to 93.8±5.6 pg/mg protein in the 10 mg/kg Felodipine group (#p<0.05), and they dropped even lower to 64.6±4.3 pg/mg protein in the 20 mg/kg Felodipine group (##p<0.01). These findings underscore the substantial anti-inflammatory properties of Felodipine.

Table 3. Biochemical parameters: MDA and TNF-α levels				
	Control	PTZ (70 mg/kg) and saline	PTZ (70 mg/kg) and 10 mg/kg felodipine	PTZ (70 mg/kg) and 20 mg/kg felodipine
Brain MDA level (nmol/gr protein)	2.8±0.3	23.7±3.02*	11.2±1.6#	9.5±0.8##
Brain TNF-alpha (pg/mg protein)	21.5±2.4	133.4±7.5**	93.8±5.6#	64.6±4.3##
Data were expressed as mean±SEM. Statistical analyses were performed by one-way ANOVA test. *p<0.05, ** p<0.001 (different from control group), # p<0.05, ## p<0.01 (different from PTZ and saline group)				

DISCUSSION

This research thoroughly assessed the anticonvulsant effects caused by Felodipine in the pentylentetrazol (PTZ)-induced epileptic seizure paradigm, along with its impact on neuroinflammation and oxidative stress. Our findings demonstrate that Felodipine significantly improves seizure severity and onset time while also reducing neuroinflammatory and oxidative processes. When evaluating the consistency of our results with other studies in the literature, the significance of these findings in epilepsy treatment is discussed.

Felodipine was shown to reduce the seizure stage on the Racine Convulsion Scale and significantly extend the start time of FMJ. This data suggests that felodipine may reduce the frequency and severity of seizures caused by PTZ. These findings parallel those of Yiu and Knaus (1996), who reported that Felodipine reduced seizure severity in the MES model (5). Saniya et al. (2019) correlated Felodipine's capacity to diminish seizure severity with its function as an inhibitor of calcium channels of the L-type (4). A study demonstrated that felodipine outperformed other CCBs in PTZ- and pilocarpine-induced seizure models. Felodipine showed superior efficacy in reducing seizure frequency and protecting against neuronal damage, offering a favorable therapeutic profile (5,6).

Felodipine's effectiveness in seizure management is attributed to its capacity to block L-type voltage-dependent calcium channels, hence diminishing intracellular calcium influx. This plays a critical role in mitigating neuronal hyperactivity and suppressing epileptogenesis processes (2). Considering the central role of calcium in seizure pathophysiology, Felodipine is thought to achieve seizure control through this mechanism (7).

Felodipine's anticonvulsant effect involves not only the inhibition of L-type calcium channels but also indirect effects on N-methyl-D-aspartate (NMDA) receptors and sodium channels. Given the role of NMDA receptors in epileptogenesis, Felodipine's potential to block these channels could be significant in reducing epileptic

brain activity (1,2). This mechanism has also been demonstrated in pilocarpine-induced seizure models, where Felodipine delayed seizure onset and reduced severity (13). Therefore, these findings are consistent with our results and suggest that Felodipine exerts its effects through various molecular pathways.

Following Felodipine administration, a significant reduction in spike activity was observed in EEG recordings. The reduction in spike percentage indicates that Felodipine can suppress the electrical activity of PTZ-induced seizures. Erbaş et al. (2015) published similar results in PTZ models, showing that antiepileptic medications greatly decreased PTZ-induced spike activity (7). These reductions in EEG activity support the ability of Felodipine to control the electrical propagation of seizures (8).

The effect of Felodipine on neuroinflammation was confirmed by a significant reduction in TNF-α levels. Neuroinflammation is a crucial factor in epileptic brains that enhances neuronal hyperactivity and epileptogenesis processes. These findings are consistent with those of Vezzani and Baram (2007), who highlighted the effects of proinflammatory cytokines on the epileptic brain (14). Our study demonstrates that Felodipine has the potential to mitigate neuroinflammation by reducing TNF-α levels.

Additionally, Felodipine's effect on oxidative stress was evaluated through a reduction in MDA levels. Oxidative stress is a major cause of cellular damage during epilepsy and plays a critical role in chronic epileptogenesis (15). The role of oxidative stress in epileptogenesis was highlighted by Rogawski and Löscher (2004), who also discussed the possibility of medications that lessen oxidative stress in the treatment of epilepsy (8). In our study, Felodipine was found to mitigate oxidative stress-related damage by lowering MDA levels (14).

Targeting these processes with pharmaceutical therapies is crucial because of the significant role that oxidative stress plays in the pathogenesis of epilepsy. Felodipine's ability to reduce lipid peroxidation and MDA levels is

notable in this context. The findings reported in our study align with other studies examining the effects of calcium channel blockers like flunarizine on oxidative stress. Clinical trials with flunarizine have shown a decrease in oxidative stress indicators in individuals with migraines, for instance (16). Similarly, Felodipine's effects expand its potential use in neurological conditions such as epilepsy and migraine.

Regarding neuroinflammation, the reduction in TNF- α levels demonstrates Felodipine's ability to alleviate seizure-induced inflammatory processes. These findings are consistent with theories suggesting that Felodipine, known as a P-glycoprotein (P-gp) inhibitor, can enhance the efficacy of antiepileptic drugs in the brain (14,17,18).

There have been comparisons between felodipine and other calcium channel blockers, including nimodipine and diltiazem, in terms of their effectiveness in controlling seizures. While nimodipine has shown promise in MES and PTZ models, its potential for adverse effects on the cardiovascular system has restricted its use in clinical practice (1). Felodipine's higher vascular selectivity and anti-inflammatory effects make it a more advantageous option for epilepsy treatment. Kamal et al. (1990) reported that calcium channel blockers are effective in seizure control and noted that Felodipine demonstrates superior efficacy in this regard (2).

Felodipine is considered to have greater vascular selectivity and a favorable safety profile compared to other calcium channel blockers, based on previous reports. Our findings support its efficacy and neuroprotective properties in the PTZ-induced seizure model. While other drugs like nimodipine are known to be effective in seizure control, their cardiovascular side effects limit their clinical applications (1,19). Felodipine's higher vascular selectivity is a critical advantage in minimizing cardiovascular side effects. Furthermore, the ability of calcium channel blockers to reduce oxidative stress and provide neuroprotective effects enhances their importance in epilepsy treatment (20).

In addition to its anticonvulsant effects, Felodipine's potential to mitigate post-seizure cognitive impairments is significant. Jansone et al. (2015) demonstrated that a novel 1,4-dihydropyridine derivative improved spatial learning and memory in animal models and highlighted the therapeutic potential of calcium channel blockers in reducing cognitive deficits during neurodegenerative processes (21). Similarly, earlier studies have reported that Felodipine reduced cognitive losses in passive avoidance learning tests under hypoxic conditions, supporting its evaluation as a potential agent for managing post-epileptic neurodegenerative outcomes (1). Although cognitive performance was not directly assessed in our study, the observed neuroprotective effects of Felodipine—such as reduced TNF- α and MDA levels—may provide a rationale for future studies to investigate its potential in mitigating post-epileptic cognitive deficits.

One of the distinguishing features of this study is its comprehensive evaluation of Felodipine's effects not only on seizure activity but also on neuroinflammatory and oxidative stress markers within the same acute PTZ-induced seizure model. While previous studies have primarily focused on Felodipine's anticonvulsant effects using behavioral or electrophysiological measures alone, our study integrates behavioral scoring (Racine scale and FMJ latency), EEG-based spike analysis, and biochemical quantification of TNF- α and MDA levels. This multimodal approach allows for a more holistic understanding of Felodipine's dual action—both seizure-suppressing and neuroprotective—within a single experimental framework. Furthermore, unlike earlier reports that often compare Felodipine with other calcium channel blockers without simultaneously measuring markers of inflammation or oxidative stress, our study directly assesses these neurobiological processes, providing stronger mechanistic insights.

Our study presents a comprehensive approach by evaluating the anticonvulsant and neuroprotective effects of Felodipine at both behavioral and biochemical levels. However, this study is limited to an acute seizure model, and the efficacy of Felodipine in chronic epilepsy models remains unexplored. Additionally, whether its neuroprotective effects persist with long-term use warrants further investigation. This study was conducted using an acute PTZ-induced seizure model in rats, which may not fully mimic the complex and chronic nature of human epilepsy. Additionally, the long-term effects and safety of Felodipine in chronic seizure models or clinical settings were not assessed. Future studies should explore its sustained efficacy, optimal dosage, and potential interactions with other antiepileptic medications in both chronic models and clinical trials.

This study concludes by demonstrating Felodipine's potential as a potent neuroprotective and anticonvulsant drug in the PTZ-induced seizure model. By reducing seizure severity, delaying seizure onset, and mitigating neuroinflammatory and oxidative stress processes, Felodipine demonstrates its ability to address multiple pathological mechanisms underlying epilepsy. Its dual-action mechanism, targeting both L-type calcium channels and other molecular pathways, provides a promising foundation for its therapeutic application. Furthermore, the significant reductions in TNF- α and MDA levels emphasize its role in minimizing secondary neuronal damage and improving long-term outcomes. These findings, supported by Felodipine's previously reported vascular selectivity and lower side effect profile compared to other calcium channel blockers, suggest its potential utility as a safer and more versatile option for epilepsy management (19). Nonetheless, additional research is required to assess its effectiveness in chronic epilepsy models and its enduring neuroprotective advantages to comprehensively determine its clinical significance in epilepsy management.

CONCLUSION

In conclusion, this study provides robust evidence supporting the anticonvulsant and neuroprotective potential of Felodipine in a PTZ-induced acute seizure model. Through comprehensive behavioral, electrophysiological, and biochemical analyses, Felodipine was shown to significantly reduce seizure severity, delay seizure onset, and attenuate both neuroinflammation and oxidative stress. These findings suggest that Felodipine exerts a dual mechanism of action by modulating calcium influx via L-type calcium channels and suppressing pathophysiological processes underlying epileptogenesis. Given its favorable safety profile, vascular selectivity, and ability to cross the blood-brain barrier, Felodipine emerges as a promising candidate for repositioning in epilepsy management. Nonetheless, further studies in chronic epilepsy models and clinical trials are warranted to evaluate its long-term efficacy, cognitive outcomes, and potential synergistic effects with existing antiepileptic drugs.

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Investigation of Demographic Characteristics and General Appearance of Individuals with Angelman Syndrome

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Abstract

Aim: Angelman syndrome (AS) is an autosomal dominant neurogenetic condition seen in 1 in 10000-22000 as a result of UBE3A gene dysfunction and microdeletion of the 15q11-13 region. The aim of this study is to determine the differences and similarities between individuals with AS by evaluating the demographic characteristics and general appearance of patients diagnosed with AS.

Material and Method: Age, gender, weight, height, BMI, weight, height and head circumference at birth, age of parents, type of birth, mother's gestation period, relationship status of mother and father, presence of genetic disease, dead or miscarried siblings number, parental smoking status, first appearance of clinical signs of the disease, epilepsy, scoliosis, sleep, nutrition, and speech problems, laughing attacks, tongue size, gait status, hair and eye color of 79 cases with genetic diagnosed AS case were evaluated.

Results: Of the individuals with AS who participated in the study, 40 (50.6%) were boys and 39 (49.4%) were girls. 43 of the patients (54.4%) were walking. The earliest walker among these patients started walking at the age of 3, and the latest walker started walking at the age of 13. 31 (40.5%) of our patients started walking between the ages of 3 and 4. When we asked the families when they noticed the first symptoms, all families realized that there were developmental problems before the child was 24 months old and consulted a physician. In fact, 70 of the families (88.6%) understood the problem before 12 months. When the time of onset of symptoms in boys and girls was compared, it was seen that the onset of symptoms was on average 2.82 months earlier in boys than in girls ($p=0.004$). The majority of cases with AS were thin, fair-skinned and blue-eyed individuals.

Conclusion: The parameters evaluated in our study revealed general and current data about the characteristics of individuals with AS.

Keywords: Angelman syndrome, general appearance, clinical features, UBE3A gene, microdeletion

INTRODUCTION

Angelman syndrome (AS) is an autosomal dominant neurogenetic condition seen in 1 in 10000-22000 as a result of UBE3A gene dysfunction and microdeletion of the 15q11-13 region. The syndrome was first described in 1965 by a British Pediatrician, Dr. Described by Harry Angelman. Although clinical findings vary from person to person, developmental delay, mental retardation, laughing attacks, epilepsy, autism spectrum disorder, hypotonia, bradykinesia, feeding and sleep disorders, hearing, speech and vision problems, and musculoskeletal system diseases are generally observed. The disease is also called 'Happy Puppet Syndrome' due to the presence of a constantly smiling facial expression in patients (1,2).

AS has different genetic mechanisms such as uniparental disomy, imprinting defect, UBE3A gene mutation and deletion. The most common of these is microdeletion, which occurs in 70-75% (3). Experimental studies have shown that UBE3A gene mutation causes synaptic and cellular changes in various parts of the brain (4).

In cases of AS, no abnormalities are observed before or during birth. The first symptoms of the disease occur at ages 6-12. It begins with developmental delay between months and months. Speech may be limited to a few words or not at all. During these periods, patients laugh excessively and have a constantly smiling facial expression (3). During these periods, families apply to the hospital thinking that there is a problem with the child.

CITATION

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The definitive diagnosis is made as a result of genetic examination. It is similar to Rett Syndrome in terms of clinical findings. For this reason, genetic examination is very important (5). There are some important criteria in making a diagnosis. Of these, epilepsy and the presence of seizures starting before the age of three, abnormal electroencephalography (EEG) results and microcephaly are seen in 80% of individuals with AS. Craniofacial features such as flat occiput, wide mouth, widely spaced teeth, protruding tongue, feeding problems, sucking/swallowing disorders, strabismus, hypopigmented skin according to family members, light hair and eye color, hyperactive lower extremity deep tendon reflexes, obesity (in older children; It is more common in those without 15q11.2-q13 deletion), clinical findings such as scoliosis and constipation are among the diagnostic criteria seen in individuals with AS. Metabolic, hematological and chemical laboratory findings are normal in the disease, and brain imaging findings are also normal, but mild cortical atrophy or dysmyelination may be observed (6).

There is no clear treatment for the disease. However, treatment methods have been developed to reduce or prevent existing problems. Anti-seizure medications are needed for epilepsy, physical therapy and rehabilitation are needed for musculoskeletal disorders and special education is needed for behavioral problems (7-9).

In line with this information, we aimed to determine the differences and similarities between individuals with AS by evaluating the demographic characteristics and general appearance of patients diagnosed with AS in our study.

MATERIAL AND METHOD

Study of data was collected by interviewing the families of individuals with AS in different cities of Türkiye in the Angelman Türkiye Community. First of all, consent was obtained from the families, who agreed to share their children's information completely. Then, data were collected by interviewing 82 families. However, 3 children with AS with missing information were excluded from the study. The cases were patients who went to the hospital regularly and did not miss their check-ups since their diagnosis. Therefore, all the data we wanted to access was available in the patients' files.

The case's age, gender, weight, height, body mass index (BMI), weight, height and head circumference at birth, age of parents, type of birth, mother's gestation period, relationship status of mother and father, presence of genetic disease, number of siblings, dead or miscarried sibling, information about the number of children, their parents' smoking status, age at first appearance of clinical signs of the disease, epilepsy, scoliosis, sleep, nutrition, speech problems, laughing attacks, tongue size, and walking status were evaluated. At the same time, hair and eye color were evaluated regarding the child's physical appearance. It was also questioned at what age the patient was diagnosed and whether he received special educational support.

Statistical Analysis

Data were evaluated with IBM SPSS V.29. Descriptive statistics were given as mean and standard deviation for normally distributed data, median, quartiles and minimum-maximum values for non-normally distributed data. Categorical data were summarized with numbers and percentages. Independent samples t test was used to determine the relationship between two averages. In statistical analysis, the significance level was considered as $p < 0.05$.

RESULTS

Of the individuals with AS who participated in the study, 40 (50.6%) were boys and 39 (49.4%) were girls. The average age of the participants was 11.82. When the presence of a genetic disease in their relatives was questioned, it was seen that only 8 (10.1%) had a genetic disease in their first or second degree relatives, while the remaining 64 (89.9%) patients did not have any genetic disease in their relatives.

According to the frequency analysis 51 (64.6%) of the cases were born by cesarean section and 28 (35.4%) were born by vaginal birth. Most patients had a normal gestational age (Table 1).

The birth weights of the patients were evaluated. There were 13 (16.5%) cases weighing less than 2500 grams. There were 2 (2.6%) cases born weighing 4000 grams and above. The weight of 54 of the cases (80.9%) was between 2500 and 4000 grams. The maximum birth weight of the patients was 4600 grams and the minimum value was 1300 grams. The average birth weight was calculated as 2979,43 grams. Considering their height at birth, 12 (11.4%) cases were born with a height of 45 cm or less. The maximum birth height of the patients was 61 cm and the minimum value was 43 cm. The average birth height was calculated as 50.05 cm. When the head circumference at birth was evaluated, the head circumference of 59 (74.7%) of the cases was 35 cm or less.

When the ages of the mother and father were evaluated at the time of birth, there were 15 (19%) mothers who were 35 and over, while the majority of mothers' ages were between 20-34 years. When the ages of the fathers were evaluated, there were 56 (70.9%) fathers aged 35 and under, while there were 23 (29.1%) fathers over the age of 35. When the smoking status of the mother and father was questioned, 14 of the mothers (17.7%) and 40 of the fathers (50.6%) were smokers. When the kinship status between the patients' mothers and fathers was evaluated, 5 (6.3%) were close relatives and 10 (12.7%) were distant relatives. There was no consanguineous relationship between the parents of 64 (81%) patients. When the number of miscarriages experienced by the patient's mothers before was evaluated, 20 of the mothers (25.3%) had experienced 1 miscarriage and 3

of them (3.8%) had a history of 2 miscarriages. 56 of the mothers (70.9%) had no history of miscarriage.

All patients were diagnosed with AS in genetic analysis. When we asked the families when they noticed the first symptoms, all families realized that the child had developmental problems before the child was 24 months old and consulted a physician. According to the frequency analysis, 70 of the families (88.6%) had understood the problem within 12 months (Table 2). When the time of onset of symptoms in boys and girls was compared with Independent samples t test, it was observed that there was a significant difference between the age at which the first symptoms were noticed in male and female patients. It was seen that the onset of symptoms was on average earlier in boys than in girls ($p=0.004$).

It took time for the family to realize the situation, consult a doctor and make a clear diagnosis. According to the frequency analysis when the age at diagnosis of the patients was evaluated, the earliest diagnosed patient was 1 year old, while the latest diagnosed patient was 14 years old (Table 3). There was no significant difference in age at diagnosis between boys and girls.

While 66 (83.5%) of the patients were also diagnosed with epilepsy, 64 of them frequently had seizures. There was no history of seizures or epilepsy in 13 of the patients (16.5%). Laughing attacks, feeding and sleeping problems, and hyperactivity status of the patients are shown in the table (Table 4).

Only 3 of the patients (3.8%) could speak. Others had a limited number of word outputs. While 44 of them could make monosyllabic sounds, the others (37) could make an average of 5 to 10 words. When male and female patients were compared, it was observed that male patients had an average of 5.23 words and female patients had 1.77 words on average, but there was no statistically significant difference between them ($p=0.136$). 43 of the patients (54.4%) were walking, and the earliest among these patients started walking at the age of 3, while the latest walked at the age of 13. 31 (40.5%) of our patients started walking between the ages of 3 and 4. 27 of the patients (34.2%) had scoliosis. We also found that 20 (25.3%) of the patients had larger than normal tongue sizes and had drooling problems. When the hair and eye color of the patients were evaluated, we saw that there were more patients with brunette and blue eyes (Figure 1, Figure 2).

As a result of the BMI scores calculated by evaluating the weight and height of the patients, the average BMI value of the patients was calculated as 19.21. 40 (50.6%) of the patients were underweight, 24 (30.4%) were normal, 11 (13.9%) were overweight, 2 (2.5%) were 1st degree obese, 2 were (2.5%) was found to be 2nd degree obese.

Table 1. Pregnancy period; Pregnancy periods and distribution are given in the frequency analysis table

Pregnancy week	Frequency	Percent (%)
41	6	7.6
40	22	27.8
39	10	12.7
38	19	24.1
37	7	8.9
36	4	5.1
35	3	3.8
34	4	5.1
33	1	1.3
31	1	1.3
30	1	1.3
28	1	1.3

Table 2. Months when the family first noticed the problems and consulted a physician

The month	Frequency	Percent %
1	16	20.3
2	2	2.5
3	3	3.8
4	5	6.3
5	8	10.1
6	15	19.0
7	5	6.3
8	5	6.3
9	4	5.1
10	4	5.1
11	3	3.8
13	1	1.3
14	3	3.8
15	1	1.3
18	2	2.5
20	1	1.3
24	1	1.3
Total	79	100.0

Table 3. Age at diagnosis

Age	Frequency	Percent %
1	27	34.2
2	22	27.8
3	1	1.3
3	17	21.5
4	7	8.9
5	1	1.3
6	2	2.5
12	1	1.3
14	1	1.3
Total	79	100.0

Table 4. Laughing attacks, feeding and sleeping problems, presence of hyperactivity in patients								
	Feeding problems		Sleep problems		Laughing attack		Hyperactivity	
	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
Yes	51	64.6	65	82.3	52	65.8	63	79.7
No	28	35.4	14	17.7	27	34.2	16	20.3

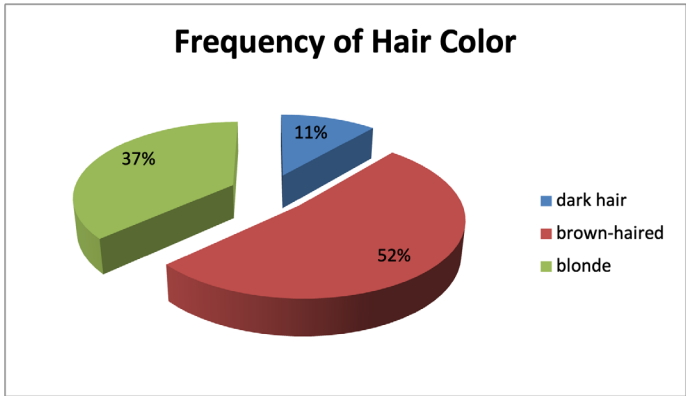


Figure 1. Hair color of patients

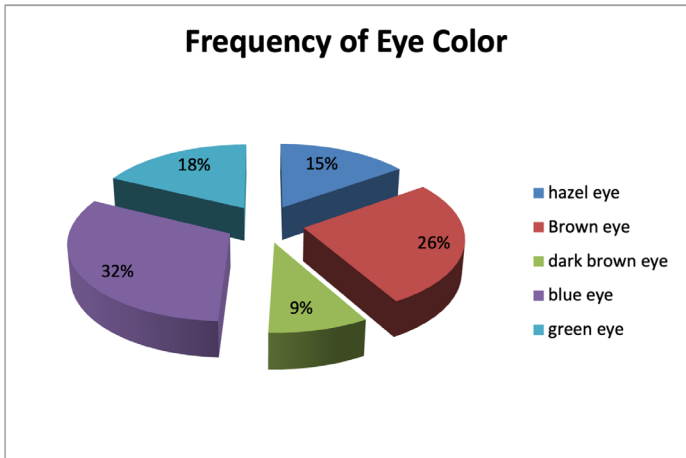


Figure 2. Eye color of patients

DISCUSSION

In this study, demographic information and general appearance of 79 patients diagnosed with AS were evaluated. At the same time, the differences and similarities between individuals with AS are emphasized. The fact that there are few studies on this subject or that the studies are mostly in the form of case reports adds value to our article.

According to a study conducted in 2022, the first studies on AS started in 1965. Genetic research accelerated in 1993. To date, 2663 studies on this subject have been added to the literature (10).

In a cohort study conducted with a literature review, 48 male and 47 female cases were included and the average age was reported as 31.6 years (11). In a study conducted in China where 577 cases of individuals with AS were evaluated, the average age was calculated as 6.34±2.94 years. No significant difference was found between age and gender (12). In a study where 100

patients diagnosed with AS, 50 girls and 50 boys, were evaluated between 2010 and 2017, the average age was 5.7 years (13). In our study, the ratio of girls to boys was similar and the average age was 11.82. Although the average age in our study is consistent with some studies in the literature, it is expected to differ from some studies and vary depending on country and time.

The genetic basis of the disease suggests that genetic diseases in the family should be questioned. In a study, only 17 of 577 patients were found to have a genetic disease in their family (12). In our study, genetic disease was found in the first and second degree relatives of only 8 of our patients. This may be explained by the fact that the disease is rare and less likely to come from the mother or father.

An 11-year-old case reported in 2021 weighed 3600 grams. It was observed that the baby was born normally and there were no problems in the prenatal period (14). Akça et al examined 5 cases in a study. One of these cases had a diagnosis of Prader Willi syndrome. All cases were born normal and on time (15). In another study, the average birth weight of 80 cases whose birth weights were reached was reported as 3.117gr (11). In a study evaluating a 7.5-year-old case, it was stated that the patient's weight, height and head circumference measurements at the time of birth were within normal values (16). 92% of the 87 cases for which information was available during pregnancy were term babies. Of the cases we evaluated, 80.9% were of normal weight and 88.6% were of normal height at the time of birth. The majority of cases diagnosed with AS are no different from normal babies at the time of birth. It is a disease that is noticed by delayed development in the first few years. For this reason, our data were found to be compatible with the literature.

In our study, the gestational ages of the mothers were concentrated between 20 and 34. There were 19% mothers over the age of 35. In another study, the gestational ages of the mothers ranged between 26 and 39 (11). The increase in the age of marriage also results in an increase in the gestational age. In this case, advancing age brings with it risky pregnancies. In our study, when the mothers were questioned about their miscarriage pregnancies, it was seen that 29.1% had a history of 1 or more miscarriages. In one case reported by Knezevic et al., the mother had a previous history of miscarriage (9).

The diagnosis of the disease, which begins with developmental delay, is confirmed by genetic screening. In this case, the family, realizing that the development has passed, consults a physician. Early recognition by the family enables the diagnosis to be made earlier. In our cases, families noticed developmental problems before the child was 24 months old and consulted a physician. In a study conducted in 2021 with people who cared for individuals with AS for a long time, it was seen that the first ones to notice the symptoms were mostly caregivers and their complaints were compatible with the physician's diagnosis (8). In one reported case, the first symptoms were noticed by the family at the 6th month and the diagnosis was made at the age of (2,9). In another case, the patient's first symptoms were noticed by the family when she was 13 months old, and the age of full diagnosis was 7.5 years old (16). In a study evaluating 95 cases, it was stated that the first symptoms of 82% of the cases began to appear in the first few months and the average age of diagnosis was 6.8 years (11). The average age at diagnosis of 219 cases, aged between 0-18, was 6 months (17). With the advancement of technology, increased doctor's checks and increased awareness of families, diseases with a genetic basis are diagnosed at an earlier age.

Epilepsy is a very common clinical condition in patients with AS. In a study, 55% of the patients had epilepsy, while in another study, 82% of the patients were diagnosed with epilepsy (12,13). In a study examining 265 cases aged between 0 and 18, 46 cases did not experience seizures. Among 219 cases, 54% were diagnosed with AS before their first seizure (17). In another reported case, it was stated that there was no epileptic seizure and no diagnosis of epilepsy was made (9). In our study, most of the patients (83.5%) were diagnosed with epilepsy. The diagnosis of epilepsy, which is seen in most cases of AS, may not be seen in some cases.

Feeding and sleeping problems, laughing attacks, hyperactivity and scoliosis are among the common findings in patients with AS. In a study published in 1995, the clinical findings seen in all AS individuals were classified as developmental delay, speech disorder, balance and coordination problems, behavioral disorders, laughing attacks, stereotypical movements, and short attention span (18). When the studies were examined, cases where these findings were observed frequently were found (9,11). In a study evaluating 94 cases, 50 of the patients had scoliosis (11). In another study, 17.5% of cases had scoliosis (12). Scoliosis developed at different levels and degrees in 34.2% of our cases.

In a study 100 patients were evaluated. In the study, it was reported that all patients had feeding problems and 13 patients even required tube feeding before or at that time (19). Our cases had similar nutritional problems.

Sleep problems were present in 81 of 92 cases whose information was obtained in the studies (11). In another

study, the rate of people with sleep problems was reported to be 91% (13). In a systematic review in which 14 studies were analyzed, data from 133 female and 133 male patients were evaluated. The sleep problems of the patients were investigated and it was stated that they had many problems with falling asleep, wakefulness, and sleep duration (20). Consistent with the literature, there were 82.3% of patients with sleep problems in our study.

Developmental delay in patients with AS causes them to walk and talk later. In our cases, 54.4% of the patients were walking, and the earliest among these patients started walking at the age of 3, while the latest walked at the age of 13. 40.5% of our patients started walking between the ages of 3 and 4. In a study, 65% of 92 cases were walking independently. There were 13% cases who walked with support and 22% who could not walk at all (11). In studies, the average walking age of patients diagnosed with AS was found to be 2.6 years, 5.125 years, 2 years, 3 years, 2.9 years (21-26). The diagnosis of the disease, the patient's age and development, and the age at which physical therapy begins directly affect the patient's walking status. The difference in findings in the studies may be due to these situations. For this reason, every child diagnosed with AS should undergo a detailed physical examination and, if necessary, physical therapy and rehabilitation should begin at the earliest. When the speech status of the patients was evaluated, in one study, 20 out of 92 cases could not speak at all. But others could say even a few words (11). In another study, there was no word output in 80.24% of the cases. Only 0.87% could speak short sentences (12). Similarly, in our study, the majority of patients could not speak, while others could say monosyllabic or simple words. The frequency of speech problems seen in individuals with AS indicates that speech-language therapy should be started after diagnosis.

Studies have shown that hair, skin and eye color may be lighter in individuals with AS (27). When the general characteristics of individuals with AS were examined, it was reported that 88% had blue eyes and 65% had blonde hair (14). In the study of Lossie et al., the rate of patients with light skin and light hair was found to be 20%, while in the study of Payatos et al., this rate was reported as 33% (21,22). Another study reported that 77.30% of cases had light skin color (12). Unlike the literature, we evaluated the hair and eye colors of the patients. Our data similarly showed that patients had lighter skin. The majority of our patients were brown-haired (52%) and blonde (37%), and their eye colors were blue (32%).

The patients' weight and height were recorded and their BMI was calculated. According to these calculations, the majority of our patients (50.6%) were found to be underweight. In studies, the weights of patients were evaluated and a rate of 33.3% to 20% of obese cases was found (21-26). The average weight of 78 cases is 68 kg. There were 45 cases with normal BMI, 4 underweight cases, 20 overweight cases and 9 obese cases (11).

In this syndrome, maternal pregnancies are generally normal and birth weights are no different from normal. However, they may be underweight due to subsequent nutritional problems (28). In our study, the large number of cases that were young and had nutritional problems caused their weights to be low.

Today, there is still no treatment that provides repair of the chromosomal defect and restoration of the mutant gene. Ultimately, treatment focuses on the patients' neurological and physical problems. For this reason, treatment is symptomatic. Training and rehabilitation provided to increase the comfort of life of patients are the most important forms of treatment and a multidisciplinary approach is required in these treatments (15). All patients in our study received physical therapy, age-appropriate speech therapy and special education support. Studies have shown that alternative therapies such as massage and aromatherapy help increase concentration and reduce hyperactivity (15).

CONCLUSION

In our study, the demographic information and general characteristics of 79 individuals with AS were evaluated and the similarities and differences between them were noted. All cases evaluated were individuals who did not experience any problems during and at the time of birth. Additionally, most of our patients were fair-skinned and blue-eyed children. The diagnosis process usually started when the family consulted a physician due to developmental delay. For this reason, it is very important for families to be aware, to take into account the developmental delays seen in infancy and not to neglect the necessary medical check-ups.

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Additive Benefit Analysis of Spinal Discectomy Tissue Specimens

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Abstract

Aim: The necessity of performing routine histopathological examinations on intervertebral disc specimens obtained during microdiscectomy remains a matter of debate with limited data available in the current literature. This study aimed to evaluate whether such routine examinations provide additional diagnostic or therapeutic value.

Material and Method: A total of 224 intervertebral disc specimens (78 cervical, 146 lumbar) obtained from 190 consecutive patients who underwent surgery for symptomatic disc herniation between 2017 and 2021 were retrospectively analyzed. Clinical, radiological, intraoperative, and histopathological findings were systematically analyzed and compared.

Results: The most frequently affected levels were C5–C6 and C6–C7 in the cervical spine, and L4–L5 and L5–S1 in the lumbar spine. A statistically significant difference was observed in the type of herniation between the cervical and lumbar regions ($p=0.0005$). Histopathological examination revealed degenerative changes in all specimens. In one case, polymorphonuclear cell infiltration was noted; however, there were no supporting clinical or radiological signs suggestive of discitis. In another case, the intraoperative discovery of black disc material led to a diagnosis of alkaptonuria, which was later confirmed by genetic analysis.

Conclusion: Routine histopathological examination of intervertebral disc specimens obtained during microdiscectomy did not contribute to diagnosis or treatment planning in our study. Given the low diagnostic yield and additional cost, such evaluations should be reserved for selected cases with specific clinical, radiological, or intraoperative suspicion.

Keywords: Microdiscectomy, histopathological examination, intervertebral disc, degenerative disc disease, cost-effectiveness

INTRODUCTION

Intervertebral discs (IVDs) are fibrocartilaginous structures located between the vertebral bodies, contributing to both the load-bearing capacity and flexibility of the spine. Unlike other connective tissues, IVDs begin to show degenerative changes early in life. The development of disc herniation is primarily influenced by factors such as aging, mechanical stress, repetitive microtrauma, genetic predisposition, and alterations in the biochemical composition of the disc. Histopathologically, this process is characterized by disorganization of collagen fibers, loss of glycosaminoglycans, fibroblastic proliferation, inflammatory cell infiltration, and endochondral ossification (1-4).

Degenerative changes compromise the mechanical integrity of the disc, increasing its susceptibility to herniation. The severity of clinical symptoms is generally

associated with the direction of disc herniation, its impact on neural structures, and the degree of the inflammatory response (1,2,5). Although intervertebral disc herniations (IVDHs) manifest with distinct clinical presentations depending on their anatomical location, they share similar pathophysiological mechanisms (2,3). Cervical, thoracic, and lumbar disc herniations produce varying clinical pictures depending on regional anatomy and the involvement of adjacent neural elements (6-10). Herniations at the cervical and thoracic levels may cause spinal cord compression due to the narrower canal diameter, often leading to cervical or thoracic myelopathy. Additionally, foraminal narrowing may result in radiculopathy symptoms (4-6,11). In contrast, since the spinal cord terminates in the lumbar region, lumbar disc herniations typically compress nerve roots, presenting with symptoms such as sciatica, low back pain, and functional impairment in the lower extremities (11-15).

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Histological studies have shown that structural degeneration of the IVD can begin as early as childhood, even around the age of 11 (3,16). This degenerative progression compromises the biomechanical integrity of the disc over time and clinically manifests as neck and back pain (2,14,16). Low back pain affects approximately 80% of the population at some point in their lives, while neck pain affects around 20% (6,17-19). Although most patients improve with conservative management, about 2–10% eventually require surgical intervention (7,11,14,15). The treatment of IVDH includes conservative modalities such as physical therapy, epidural injections, and surgical interventions, including microdiscectomy, decompression, disc replacement, or spinal fusion. Microdiscectomy is a commonly preferred surgical technique in the presence of radiculopathy or neurological deficit, with reported success rates ranging between 80% and 90% (11,14).

Histopathological examination of disc material obtained during surgery is typically performed to rule out rare malignancies and infections, as well as to fulfill medicolegal documentation and institutional protocols. However, several studies have questioned the clinical utility of routine pathological evaluation in cases of benign disc herniation, suggesting its limited contribution to patient management (4,16,20).

This study aims to systematically assess whether histopathological analysis of disc specimens obtained from cervical and lumbar microdiscectomy cases performed for degenerative disc disease, trauma, spondylolisthesis, spondylolysis, spinal stenosis or spondylosis offers any diagnostic or therapeutic value in the clinical decision-making process. By doing so, we seek to objectively evaluate the role and necessity of routine pathological assessment in contemporary spine surgery practice.

MATERIAL AND METHOD

Between January 2017 and October 2021, all histopathological reports of intervertebral disc specimens obtained by a single surgeon at a single tertiary care center were retrospectively reviewed. Patients with a preoperative clinical suspicion of infection or malignancy were excluded from the study. Particular attention was paid to any histopathological findings that altered the course of clinical management. For each patient, preoperative diagnoses, intraoperative findings, and postoperative discharge diagnoses were reviewed and compared.

The study protocol was approved by the Ethics Committee of Kanuni Sultan Süleyman Research and Training Hospital (Approval Date: November 26, 2021; Approval Number: 2021.11.286). All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to present means and

standard deviations for continuous variables and frequencies with percentages for categorical variables. Comparisons between cervical and lumbar disc herniation groups were made using the independent samples t-test for age and the Chi-square test for categorical variables. Fisher's exact test was applied when expected cell counts were below 5. A p -value < 0.05 was considered statistically significant.

RESULTS

A total of 190 patients who underwent surgery for symptomatic intervertebral disc herniation were included in the study, comprising 78 cervical and 146 lumbar cases. The mean age of the cervical group was 48.2 ± 9.6 years, while the lumbar group had a significantly higher mean age of 52.5 ± 11.4 years ($p = 0.0032$). The proportion of male patients was 53.8% in the cervical group and 60.3% in the lumbar group, with no statistically significant difference between groups ($p = 0.4315$).

Based on Magnetic Resonance Imaging (MRI) findings, the most common type of herniation in the cervical region was protrusion (62.8%), followed by extrusion (26.9%) and sequestration (10.3%). In contrast, extrusion was the predominant type in the lumbar group (48.6%), followed by protrusion (35.6%) and sequestration (15.8%). The distribution of herniation types differed significantly between the two regions ($p = 0.0005$). Anatomically, the most frequently affected levels were C6–C7 (42.3%) and C5–C6 (33.3%) in the cervical spine, and L5–S1 (48.3%) and L4–L5 (35.9%) in the lumbar spine. Less frequently involved levels included C4–C5 (17.9%), C3–C4 (6.4%), and C7–T1 (0.0%) in the cervical region, and L3–L4 (10.3%), L2–L3 (6.1%), and L1–L2 (0.0%) in the lumbar region. Multilevel disc herniation was observed in 14.1% of cervical and 19.9% of lumbar cases, without a statistically significant difference ($p = 0.3738$). Similarly, the rates of severe spinal canal stenosis were comparable between the groups (cervical: 21.8%, lumbar: 23.3%; $p = 0.931$) (Table 1).

Intraoperative findings documented in surgical records included sequestered or protruding disc fragments, free disc material compressing nerve roots, osteophytic formations, ligamentum flavum hypertrophy, and varying degrees of spinal stenosis. No findings suggestive of infectious or malignant pathology were noted in any case.

A total of 224 disc specimens (78 cervical, 146 lumbar) were subjected to histopathological evaluation. All samples exhibited histological features consistent with benign degenerative changes, including fibrocartilaginous degeneration, fragmentation of the chondroid matrix, and fibrosis. None of the histopathological findings led to a change in clinical treatment protocol. In one case with a histopathological diagnosis suggestive of discitis, no supporting clinical, radiological, or intraoperative evidence of infection was found, and the patient was monitored without antibiotic therapy. In another case, black-colored disc material was noted intraoperatively; although histology revealed only typical degenerative features, the patient was subsequently diagnosed with alkaptonuria via genetic testing (Figure 1).

In all cervical discectomy cases, an interbody cage or disc prosthesis was implanted. In contrast, only a minority of patients in the lumbar discectomy group underwent fusion or stabilization procedures, which were performed based on the presence of preoperative or intraoperative signs of instability or spinal deformity.

Table 1. Demographic characteristics, MRI findings, and distribution of herniation types and levels in cervical and lumbar disc herniation cases				
Parameters	Intervertebral cervical disc tissue samples (n=78)		Intervertebral lumbar disc tissue samples (n=146)	
Mean age (years)	48.2±9.6		52.5±11.4	
Gender (Male %)	42 (53.8%)		88 (60.3%)	
Most common herniation type	Protrusion	(n=49, 62.8%)	Extrusion	(n=71, 48.6%)
	Extrusion	(n=21, 26.9%)	Protrusion	(n=52, 35.6%)
	Sequestration	(n=8, 10.3%)	Sequestration	(n=23, 15.8%)
Most common disc level(s)	C3–C4	5 (6.4%)	L1–L2	0 (0.0%)
	C4–C5	14 (17.9%)	L2–L3	9 (6.1%)
	C5–C6	26 (33.3%)	L3–L4	15 (10.3%)
	C6–C7	33 (42.3%)	L4–L5	52 (35.9%)
	C7–T1	0 (0.0%)	L5–S1	70 (48.3%)
Multilevel Involvement	n=11 (14.1%)		n=29 (19.9%)	
Severe canal stenosis	n=17 (21.8%)		n=34 (23.3%)	
Degenerative disc disease (DDD)	65		106	
Spondylosis	9		16	
Spondylolisthesis	1		9	
Spondylolysis	0		6	



Figure 1. Macroscopically, the nucleus pulposus removed from the L4-5 disc was black in colour

DISCUSSION

The histopathological evaluation of all specimens in this study revealed only degenerative changes, and no clinically significant pathological findings were identified that would necessitate a change in the treatment protocol. In one case of lumbar microdiscectomy at the L4–L5 level, polymorphonuclear leukocyte infiltration was observed histologically; however, the absence of any clinical or laboratory indicators suggestive of discitis eliminated the need for antibiotic therapy. In another case, black-colored disc material was noted intraoperatively. Although histopathological evaluation identified this tissue as degenerative chondroid material, further genetic testing ultimately led to a diagnosis of alkaptonuria.

These findings suggest that histopathological evaluation has limited diagnostic value and clinical significance, except in rare and exceptional cases. Therefore, the cost-effectiveness of routine histopathological analysis should be critically assessed. Routine pathological examination may provide meaningful diagnostic insights in selected cases particularly those with supporting clinical, radiological, or intraoperative suspicion but the automatic submission of all discectomy specimens for histopathological evaluation is not aligned with current clinical practice and raises concerns regarding the balance between cost and benefit. As demonstrated in this study, microscopic analysis did not alter the treatment protocol in any case, reaffirming its limited role outside of specific clinical indications. Although histopathological examination of discectomy specimens rarely yields diagnostic information, it may

be valuable in patients with preoperative suspicion of infection or malignancy and can significantly contribute to treatment planning in such cases. In a study by Hasselblatt et al. involving 2,177 intervertebral disc specimens, only three unexpected pathologies were reported: one case of cavernous malformation and two malignancies (0.1%) metastatic prostate carcinoma and diffuse large B-cell lymphoma (21). Despite these rare findings, the study concluded that routine histopathological evaluation of disc specimens during spinal surgery is both clinically justified and cost-effective. However, the methodological context of these exceptional cases warrants closer examination. The patient diagnosed with diffuse large B-cell lymphoma had MRI findings inconsistent with a typical disc herniation, while the patient with metastatic prostate carcinoma had a known oncological history and underwent surgery based solely on Computed Tomography (CT) imaging, without prior MRI. These cases underscore the importance of thorough preoperative evaluation and selective pathological analysis, rather than routine application in all disc surgeries. The exceedingly low diagnostic yield of routine histopathological evaluation of discectomy specimens has also been supported by previous large-scale studies. Daftari et al. analyzed 506 disc levels in 394 patients and estimated that, after 506 consecutive negative results, the likelihood of encountering a positive pathological finding was approximately 0.6% (22). Similarly, the incidence of unexpected and clinically significant histopathological findings in disc specimens obtained during discectomy for benign indications has been reported to be as low as 1 in 10,000 (16). In a retrospective review of 1,109 cases, it was concluded that histopathological evaluation of intervertebral disc specimens contributed meaningfully to clinical decision-making only when there was significant preoperative clinical suspicion of an underlying diagnosis (23). In another study analyzing 1,775 routine and 70 non-routine discectomy specimens, the authors explicitly stated that routine histopathological examination is unnecessary in cases without specific clinical indications (20). Similarly, Keller et al., in their retrospective study involving 1,387 patients who underwent cervical or lumbar discectomy, concluded that pathological examination of herniated nucleus pulposus removed during decompressive surgery was not required (24). Supporting these findings, Boutin et al., in a series of 508 laminectomy patients, demonstrated that routine pathological evaluation of disc material had no significant impact on clinical management (13). The consistent findings across multiple studies support the premise that routine histopathological analysis of disc specimens obtained during standard microdiscectomy for degenerative pathology offers extremely limited clinical benefit and may not be justifiable in terms of cost-effectiveness. Therefore, a more selective, indication-focused approach is recommended to optimize resource utilization in spinal surgery. The intraoperative observation of black disc material allowed for further metabolic evaluation, ultimately leading to a diagnosis of alkaptonuria. Based on current evidence, routine histopathological examination of intervertebral disc specimens appears unnecessary (16,24).

The decision to submit disc material for pathological analysis should be based on a combination of clinical presentation, laboratory and radiological findings, and intraoperative observations. Spine surgeons experienced in microsurgical techniques can often recognize disc tissue macroscopically with ease, and routine submission of specimens for pathological evaluation may not be necessary in every case (4,16,20). In an era of increasing demand for healthcare services, efficient and responsible use of available resources is of critical importance. Indeed, many hospital protocols already provide clear guidelines regarding which types of surgical specimens should be submitted for histopathological examination. Pathological examination performed by a pathologist cannot directly confirm whether the submitted specimen was truly obtained from a herniated disc, whether the disc was indeed herniated, or whether it was responsible for the patient's clinical symptoms. At best, histopathological analysis can serve as indirect evidence that disc tissue was removed during surgery (16,20). In modern healthcare systems, providing cost-effective and high-quality care has become a central priority. Cost-effectiveness is now recognized as a critical component of patient management. Although the primary aim of this retrospective study was not to assess the cost-effectiveness of routine pathological analysis of disc specimens, the associated economic burden warrants consideration. The routine submission of surgical specimens for histopathological analysis may be driven by institutional, insurance, or medicolegal policies aiming to document the physical removal of tissue during surgery. While identification of removed material in operative reports or intraoperative radiographic imaging may provide some degree of verification, these methods cannot always be accepted as definitive physical evidence. Alternatively, more cost-effective medicolegal documentation methods—such as photographing the disc specimen, labeling it with patient identifiers, and preserving it for potential presentation to the patient or family—may be adopted. Nevertheless, institutional surgical practices and laboratory protocols should be periodically re-evaluated on a case-by-case basis. Cervical discectomies, typically performed via an anterior approach, allow for direct and comprehensive visualization of the disc, whereas lumbar discectomies are generally carried out posteriorly and offer more limited disc exposure (7,11). However, in general, neural structures are more readily visualized in lumbar surgeries compared to anterior cervical approaches. In the absence of clear clinical indications, it is not always possible for surgeons to anticipate or identify occult pathological processes in surgical specimens. Additionally, when bone or endplate material is submitted along with the disc specimen, additional laboratory charges may be incurred.

Limitations of this study include a relatively small sample size, its retrospective single-center design, the exclusion of thoracic disc herniations (which account for less than 1% of surgical cases), and the use of standard histopathological

protocols mandated by the national health system. Furthermore, the study did not assess neuroinflammatory markers or other biochemical indicators, and all surgeries were performed by a single surgeon. A formal cost-benefit analysis was also not conducted.

CONCLUSION

The routine submission of disc specimens for histopathological examination serves as a medicolegal safeguard for the surgeon, providing the only tangible intraoperative evidence beyond radiological findings. Nonetheless, the decision to request pathological analysis ultimately remains at the discretion of the operating surgeon.

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Prevalence of Exercise Prescription and Clinical Justifications in Pediatric Rheumatology Patients with a Immigrant Background: A Single-Center Observational Study

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Abstract

Aim: Pediatric rheumatic diseases, such as Juvenile Idiopathic Arthritis (JIA), fibromyalgia, muscle strain, and scoliosis, can significantly impact physical function and quality of life. Exercise therapy is an effective, evidence-based approach for managing musculoskeletal symptoms in these patients, but its use in pediatric rheumatology remains underexplored. This study aimed to evaluate the prevalence of exercise prescription, the underlying clinical justifications, and demographic characteristics of pediatric rheumatology immigrant-background pediatric patients referred to a physical therapy clinic.

Material and Method: This prospective, cross-sectional study included pediatric patients with immigrant (0-22 years) referred from the pediatric rheumatology clinic to the physical therapy clinic of Ümraniye Training and Research Hospital between January 1 and December 31, 2024. Patient data, including age, gender, diagnosis, and treatment type, were analyzed using SPSS (v.26), with $p < 0.05$ considered statistically significant.

Results: A total of 190 patients were included (63% female, 37% male), with a mean age of 14.2 ± 4.3 years. Exercise prescriptions were provided to 55% ($n=105$) of the patients. Male patients had a slightly higher exercise prescription rate (59%) compared to females (53%), though this difference was not statistically significant ($p > 0.05$). Muscle strain (74%) and joint pain (69%) had the highest exercise prescription rates, while JIA patients had a lower rate (47%).

Conclusion: Exercise prescriptions are more common in non-inflammatory conditions like muscle strain and joint pain, while JIA patients receive them less frequently, likely due to concerns over joint damage and disease activity. Future studies should assess the long-term impact of exercise in this population.

Keywords: Pediatric rheumatology, exercise prescription, Juvenile Idiopathic Arthritis, muscle strain, physical therapy

INTRODUCTION

Pediatric rheumatic diseases are chronic, inflammatory conditions that begin in childhood and can affect joints, muscles, connective tissues, and internal organs. One of the most common examples of these diseases is Juvenile Idiopathic Arthritis (JIA), which can lead to long-term joint pain, movement restrictions, and functional impairment in children (1,2). In addition to JIA, non-inflammatory musculoskeletal disorders such as fibromyalgia, muscle strain, and scoliosis are also commonly encountered in pediatric rheumatology practice (3,4).

In these conditions, musculoskeletal involvement, pain, joint stiffness, and muscle weakness can significantly limit

physical activity in children, potentially leading to long-term declines in quality of life (3,5). Exercise therapy is a widely used, evidence-based, and effective treatment modality aimed at alleviating these symptoms, increasing muscle strength, maintaining joint range of motion, and improving functional capacity (5,6). Additionally, the anti-inflammatory effects of exercise have also been demonstrated in recent studies. It has been reported that regular physical activity can reduce levels of pro-inflammatory cytokines, thereby suppressing systemic inflammation and helping to control disease activity (7,8).

However, the frequency of exercise prescription and clinical decision-making processes in pediatric rheumatology

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patients can vary significantly depending on several factors. These factors include the patient's age, type of diagnosis, disease duration, and presence of comorbidities. Despite this, studies on the effectiveness of exercise therapy in children remain relatively limited, and the available data are often based on small sample sizes (9-11).

The purpose of this research is to determine the frequency of exercise prescription, the underlying clinical rationale, and population characteristics of pediatric rheumatology patients. Our hope is this study will shed light on opportunity and exercise therapy in pediatric rheumatic disease community, and provide insights that may assist in clinical decision-making and better management of pediatric rheumatology patients.

MATERIAL AND METHOD

Data Collection

This study was designed as a prospective, cross-sectional, and observational study involving immigrant-background pediatric patients referred to the physical therapy and rehabilitation clinic of Ümraniye Training and Research Hospital from the same hospital's Pediatric Rheumatology Clinic. The study included pediatric patients aged 0 to 22 years who were referred from the pediatric rheumatology clinic to the physical therapy clinic between January 1, 2024, and December 31, 2024.

Inclusion criteria included being 0 to 22 years old, being referred from the pediatric rheumatology clinic to the physical therapy clinic, and having undergone at least one physical therapy assessment. Patients who were enrolled in comprehensive rehabilitation programs, had unclear diagnoses or insufficient clinical follow-up, or had neuromuscular disorders or contraindications to exercise (e.g., progressive muscle diseases or severe cardiac insufficiency) were excluded. Additionally, patients with multisystem involvement or severe systemic diseases (e.g., cancer or organ failure), those in the acute postoperative period, and patients who were pregnant or in the postpartum period were also excluded from the study.

Demographic and clinical data, including age, gender, diagnosis type, treatment modality (exercise, medical), and other relevant clinical characteristics, were collected and recorded for each patient.

This study was approved by the Ümraniye Training and Research Hospital Ethics Committee (approval number: 54132726-000-26648 and, approval date: 19.12.2019)

and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their inclusion in the study.

Statistical Analysis

The collected data were analyzed using Microsoft Excel and SPSS (v.26) software. Descriptive statistics, including frequency, percentage, mean, and standard deviation, were used to calculate the distributions of patient age groups, diagnosis types, and treatment modalities.

For comparisons between groups, the Pearson Chi-square (χ^2) test was used for categorical variables. In cases where the expected cell frequencies were low, Fisher's Exact Test was applied. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For variables that did not show a normal distribution, non-parametric tests, including the Mann-Whitney U and Kruskal-Wallis tests, were used. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 190 pediatric rheumatology patients were included in this study. The ages of the patients ranged from 0 to 22 years, with a mean age of 14.2±4.3 years. Of these, 63% (n=120) were female and 37% (n=70) were male. Exercise prescriptions were provided to 55% (n=105) of the patients, while the remaining 45% (n=85) received only medical treatment or other non-pharmacological approaches.

The distribution of exercise prescriptions by gender is summarized in Table 1. The exercise prescription rate among male patients (59%, n=41) was 6% higher than that of female patients (53%, n=64), but this difference was not statistically significant (p>0.05).

Table 1. Exercise prescription rates by gender			
Gender	Total patients (n)	Exercise prescriptions (n)	Percentage (%)
Female	120	64	53
Male	70	41	59
Total	190	105	55

The distribution of exercise prescriptions by age and gender is presented in Table 2. The highest exercise prescription rate was observed in the 16-20 age group among male patients (68%, n=21), which was significantly higher than that of female patients in the same age group (p<0.05).

Table 2. Exercise prescription rates by age group and gender						
Age group	Female (n)	Exercise (n)	Percentage (%)	Male (n)	Exercise (n)	Percentage (%)
0-10	15	8	53	12	6	50
11-15	42	22	52	27	14	52
16-20	45	23	51	31	21	68
21+	18	11	61	-	-	-
Total	120	64	53	70	41	59

The distribution of exercise prescriptions by diagnosis type is shown in Table 3. Exercise prescriptions were most common among patients with muscle strain (74%, n=28) and joint pain (69%, n=11), while the rate was lower among

patients with JIA (47%, n=44). These findings suggest that the type of diagnosis may have a notable impact on exercise prescription rates. However, these differences were not statistically significant ($p>0.05$).

Table 3. Exercise prescription rates by diagnosis type			
Diagnosis type	Total patients (n)	Exercise prescriptions (n)	Percentage (%)
Juvenile idiopathic arthritis	93	44	47
Muscle strain	38	28	74
Joint pain	16	11	69
Scoliosis	8	5	62
Cerebral palsy	5	3	60
Fibromyalgia	6	4	67
Other (e.g., TME, FMF)	24	10	42
Total	190	105	55

Additionally, 46% (n=87) of the 190 patients received medical treatment, while the remaining 54% (n=103) were managed exclusively with exercise.

DISCUSSION

In this study, the prevalence of exercise prescription, demographic characteristics, and clinical rationale in pediatric rheumatology patients were comprehensively evaluated. A total of 190 pediatric patients were included, 55% (n=105) of whom received exercise prescriptions, while the remaining 45% (n=85) were managed with medical therapy or other non-pharmacological approaches. These findings are consistent with exercise prescription rates reported in the literature, although some studies have reported lower or higher rates (9,12,13).

In this study, 53% (n=64/120) of female patients and 59% (n=41/70) of male patients received exercise prescriptions. The exercise prescription rate was 6% higher in males than in females, although this difference was not statistically significant ($p>0.05$). Notably, the highest exercise prescription rate (68%) was observed in male patients in the 16-20 age group. This finding may reflect the higher physical activity levels and greater motivation for muscle strengthening typically seen in adolescent males (14-16).

Exercise prescription rates by age group also revealed notable trends. While only 52% of patients in the 0-10 age group received exercise prescriptions, this rate increased to 58% in the 16-20 age group. This may be due to the greater physical activity tolerance and higher muscle strength requirements in growing and developing children. Additionally, the need to maintain joint range of motion and improve muscle strength in older age groups may contribute to these findings (17,18). However, the relatively lower exercise prescription rate (61%) in the 21+ age group may indicate a lower inclination towards physical activity in this older patient population or a higher chronic disease burden (19,20).

In our study, patients with muscle strain had the highest exercise prescription rate (74%), indicating that exercise

is a fundamental component in the treatment of muscle strain and plays a critical role in the rapid resolution of symptoms (21). Similarly, a high exercise prescription rate (69%) was observed in patients with joint pain (21). In contrast, patients diagnosed with JIA had a relatively lower exercise prescription rate (47%). This finding suggests that exercise prescriptions for JIA patients are written more cautiously, likely due to the need for careful disease activity management (6). In particular, a more conservative approach may be preferred during periods of active inflammation to prevent joint damage (5). Additionally, during periods of high disease activity, JIA patients may experience increased pain and restricted movement, which can further reduce the likelihood of exercise being prescribed (6,17,18).

It is well established that exercise not only increases muscle strength but also has anti-inflammatory effects. Regular physical activity has been shown to reduce levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6), thereby suppressing systemic inflammation and helping to control disease activity. For this reason, more comprehensive and personalized exercise prescriptions may be beneficial for patients with chronic inflammatory conditions like JIA, potentially improving their long-term prognosis (7,8,22).

Strengths and Limitations of the Study

One of the main strengths of this study is its prospective design and the inclusion of a wide age range (0-22 years). Additionally, the use of real-world clinical data enhances the reliability of the findings and makes the results more applicable to clinical practice. The study's focus on patient referrals between pediatric rheumatology and physical therapy clinics also provides valuable insights into multidisciplinary care approaches.

However, this study has several limitations. First, it is a single-center study based on data from only one hospital, which may limit the generalizability of the findings. Furthermore, important factors that could influence clinical outcomes, such as patient adherence, exercise intensity,

and program duration, were not evaluated. In addition, subjective symptoms (e.g., pain levels, quality of life) and functional improvement were not included, which may restrict the ability to assess the long-term effectiveness of exercise therapy.

Finally, although the study included a wide range of diagnostic categories, the small sample sizes for certain patient groups (e.g., scoliosis and fibromyalgia patients) may limit the statistical power of the findings for these subgroups.

CONCLUSION

This study provides important findings on the frequency of exercise prescription and clinical decision-making processes in pediatric rheumatology patients. Our results indicate that exercise prescriptions are more common in non-inflammatory conditions such as muscle strain and joint pain, while exercise prescription rates are relatively lower in inflammatory diseases like JIA (1,5,6,13). This aligns with previous studies showing that exercise is a fundamental component of managing non-inflammatory musculoskeletal pain but requires a more cautious approach in inflammatory conditions due to the risk of joint damage and increased disease activity (3,21). Additionally, the higher exercise prescription rates observed in male patients suggest that gender may be a potential determinant of exercise prescription. This finding is consistent with studies indicating that adolescent males tend to have higher physical activity levels and greater motivation for muscle strengthening (14-16). However, in our study, exercise prescription frequencies varied across age groups, but most of these differences were not statistically significant. These age-related differences may reflect the well-documented decline in physical activity from childhood through adolescence and into early adulthood (17-20).

Future studies should focus on evaluating the long-term effectiveness of exercise therapy, patient adherence, and the impact on disease activity, using larger sample sizes and multicenter, prospective study designs (10,11,21). Additionally, the anti-inflammatory effects of exercise, which have been well-documented in both animal and human studies, suggest that carefully tailored exercise programs may offer significant benefits for managing chronic inflammatory conditions like JIA (7,8,22).

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Ethical approval: This study was approved by the Ümraniye Training and Research Hospital Ethics Committee (approval number: 54132726-000-26648 and, approval date: 19.12.2019) and conducted in accordance with the Declaration of Helsinki.

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Relationship of Prognostic Nutritional Index, HALP score and Inflammatory Markers with Clinical Outcomes in Children with Complicated Appendicitis

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Abstract

Aim: One of the most frequent diagnoses in children presenting with acute abdominal pain is acute appendicitis. This study aims to analyze the effectiveness of the biomarkers such as the Prognostic Nutrition Index (PNI), hemoglobin-albumin-lymphocyte-platelet (HALP) score, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in predicting complicated appendicitis in children who undergo surgery for acute appendicitis.

Material and Method: A total of 253 children who underwent surgery for acute appendicitis in our clinic between January 1, 2022, and October 1, 2024, and underwent surgery for acute appendicitis were included in our study.

Results: Among the cases, 81% (n=205) were classified in the non-complicated, while 19% (n=48) were in the complicated group. In our analysis, we found that the PNI (p=0.027) and HALP score (p=0.007) were considerably lower in the complicated appendicitis group, whereas the neutrophil-to-lymphocyte ratio (NLR) (p=0.003) and platelet-to-lymphocyte ratio (PLR) (p=0.008) were significantly higher. Correlation analysis revealed a meaningful positive association between PNI and HALP score, a mild unfavorable association between PNI and both PLR and NLR, a strong positive correlation between HALP score and both PLR and NLR and a mild positive relationship between NLR and PLR.

Conclusion: PNI, HALP score, NLR, and PLR values measured at the time of admission to the emergency services may serve as potential predictors in differentiating between complicated and non-complicated appendicitis.

Keywords: Children, complicated appendicitis, prognostic nutritional index, hemoglobin-albumin-lymphocyte-platelet score, inflammatory markers

INTRODUCTION

Acute appendicitis (AcA) is one of the leading causes of acute abdominal pain in pediatric patients (1). If not promptly treated, increasing inflammation may lead to gangrene and necrosis of the appendix, ultimately resulting in perforation. This progression complicates AcA and may be accompanied by more severe complications such as abscess formation and generalized peritonitis (1,2).

The use of scoring systems in conjunction with diagnostic tools specifically ultrasonography (USG) and computed tomography (CT) helps reduce perforation rates, hospital stays, and unnecessary surgical interventions (3). However, studies continue to focus on developing more

effective diagnostic methods to decrease the incidence of complicated appendicitis (CA) and to reduce mortality and morbidity rates, with particular emphasis on laboratory biomarkers (4).

Serum albumin is a well-known acute-phase protein that negatively correlates with conditions such as severe infection, systemic inflammation, malnutrition, and immunosuppression (5). In such clinical conditions, an elevation in platelet and neutrophil counts, a decline in lymphocyte levels, and the development of anemia are commonly observed (6). Based on these parameters, biomarkers such as the Prognostic Nutritional Index (PNI) (7,8), hemoglobin-albumin-lymphocyte-platelet (HALP) score (9,10), neutrophil-to-lymphocyte ratio (NLR), and

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platelet-to-lymphocyte ratio (PLR) (11) have been shown in various studies to be valuable in assessing an individual's immunological and nutritional status in processes associated with infection, inflammation, and malnutrition, and may be effective in predicting prognosis.

In this study, we aimed to determine whether there are significant differences and correlations between PNI, NLR, PLR, and HALP scores in pediatric CA and non-complicated appendicitis (NCA) cases, thereby evaluating the diagnostic efficacy of these biomarkers in predicting CA.

MATERIAL AND METHOD

Study Design

A retrospective descriptive cohort methodology was employed in this study. Children under the age of 18 who presented to the Aksaray University Department of Pediatric Surgery between January 1, 2022, and October 1, 2024, and who were prediagnosed with AcA based on history, physical examination, laboratory tests, USG, and, when necessary, CT, and subsequently underwent surgery, were incorporated into the study. Children who had received antibiotic treatment prior to surgery had no recorded appendix diameter on USG or CT, had non-visualized appendices, or whose pathology reports indicated lymphoid hyperplasia, fibrous obliteration, carcinoid tumor, mucocele, or parasitic infestation, as well as those with a history of previous abdominal surgery, incomplete medical records, or chronic diseases, were omitted from the study.

Data Collection

Patient details were obtained from electronically stored medical records. After applying the exclusion criteria, 253 cases were ultimately included in the study. Based on pathological or intraoperative findings, the patients were categorized as either non-complicated appendicitis (NCA; acute suppurative, acute phlegmonous) or complicated appendicitis (CA; perforated, gangrenous, or with phlegmon formation).

Gender, age at presentation, hemogram, electrolytes, renal and liver function tests, hemostasis parameters including C-reactive protein (CRP), coagulation tests (INR, PT, PTT), appendix diameter reported by USG or CT and appendix pathology report were recorded. In addition, PNI [Albumin (g/L) + 0.005x Total Lymphocyte count (mm³)], NLR (Neutrophil-to-Lymphocyte ratio), PLR (Platelet-to-Lymphocyte ratio), HALP score [(Hemoglobin (g/L) x Albumin (g/L) x Lymphocyte count (n/L)/Platelet count (n/L)] at admission were calculated and recorded.

Ethics Approval

The research was ethically approved by Aksaray University Scientific Research Ethics Committee on November 21, 2024 with decision number 2024/135.

Statistical Analysis

Data from the study were analyzed using version 23 of IBM SPSS Statistics software for Windows. To assess the

normality of numerical variables, the Shapiro-Wilk test and skewness and kurtosis values were used. For continuous variables, basic statistical analyses were reported as median and interquartile range (25th–75th percentile), while categorical variables were expressed as frequencies and percentages.

The Spearman correlation analysis test was used to evaluate the relationships between two continuous variables. The Mann–Whitney U test served to evaluate differences in continuous variables across two independent groups, as the Fisher's Exact Test was used for categorical variables. Results with p-values under 0.05 were considered significant.

RESULTS

A total of 253 patients, including 165 boys and 88 females with a median age of 12 years (IQR: 9–15) at the time of admission, were analyzed in our study. Of the cases, 81% (n=205) were classified in the NCA group, while 19% (n=48) were in the CA group. Among the NCA cases, 72.7% (n=149) were diagnosed with acute suppurative appendicitis, and 27.3% (n=56) with acute phlegmonous appendicitis. In the CA group, 85.4% (n=41) had perforated appendicitis, 10.4% (n=5) had gangrenous appendicitis, and 4.2% (n=2) had plastron appendicitis.

Regarding age and sex variables, no statistically marked variation was found between the two groups. The median (IQR) appendix diameter measured via ultrasonography or CT was 10 mm (8.85–11.00) in the CA group and 8.5 mm (7.0–10.0) in the NCA group, with a meaningful statistical importance between the groups (p<0.001) (Table 1).

The overall median (IQR) PNI value was 54.4 (46.77–60.40), whereas it was lower in the CA group at 50.17 (42.85–58.21), with a meaningful statistical disparity between the groups (p=0.027). The HALP score median (IQR) was 4.05 (2.21–7.08) overall and 3.25 (1.28–5.46) in the CA group, again showing a statistically meaningful significance between the groups (p=0.007) (Table 1).

The median (IQR) NLR and PLR values were 6.53 (3.81–12.78) and 182.41 (105.34–350.46), respectively, in the CA group, and 4.55 (2.53–8.44) and 138.42 (85.17–224.59) in the NCA group. Both NLR and PLR were to a considerable extent higher in the CA group compared to the NCA group (p=0.003 and p=0.008) (Table 1).

The median (IQR) neutrophil and platelet counts were higher in the CA group [12,385.0/mm³ (9,852.5–14,165.0) and 330,000/mm³ (261,000–371,000), respectively] than in the NCA group [10,560/mm³ (7,285–13,490) and 281,000/mm³ (221,000–364,000), respectively]. In the analysis, both neutrophil and platelet counts were found to be statistically significantly higher in the CA group (p=0.022 and p=0.024) (Table 1).

In comparison to the NCA group, the CA group exhibited significantly higher CRP levels and slightly lower sodium levels [median (IQR) CRP: 119.0 mg/L (79.75–182.75) vs. 10.75 mg/L (2.31–40.75); Sodium: 136.0 mmol/L

(134.25–138.00) vs. 137.0 mmol/L (135.0–139.0)]. Statistically meaningful disparities were found between the two groups for both CRP and sodium ($p<0.001$ and $p=0.047$). The median (IQR) PT and INR values in the CA group were 12.90 seconds (12.23–15.17) and 1.11 (1.07–1.22), respectively, while in the NCA group, they were 12.51 seconds (12.13–13.50) and 1.07 (1.02–1.14), respectively. There was a statistically meaningful significance between the CA and NCA in terms of INR but not for PT ($p=0.001$ and $p=0.39$) (Table 1).

Table 1. Comparison of demographic, laboratory and pathological findings of the two groups			
	Complicated (n=48)	Non-complicated (n=205)	
	MD (25-75 IQR)	MD (25-75 IQR)	p
Age (year)	12.0 (9.00–14.75)	12.0 (9.0–15.0)	0.90*
Appendix diameter (mm)	10 (8.85–11.00)	8.5 (7.0–10.0)	<0.001*
Hemoglobin (g/L)	12.95 (12.10–13.77)	13.50 (12.40–14.50)	0.054*
Leukocyte (/mm ³)	15315.0 (13065.0–17122.5)	13900 (10225–16975)	0.061*
Neutrophil (/mm ³)	12385.0 (9852.5–14165.0)	10560 (7285–13490)	0.022*
Lymphocyte (/mm ³)	1850.0 (987.0–2937.5)	2160.0 (1380.0–3035.0)	0.05*
Platelet (/mm ³)	330000 (261000–371000)	281000 (221000–364000)	0.024*
C-Reactive protein (mg/L)	119.0 (79.75–182.75)	10.75 (2.31–40.75)	<0.001*
Albumin (g/L)	40.00 (36.12–45.67)	43.1 (38.95–46.75)	0.05*
Sodium (mmol/L)	136.0 (134.25–138.00)	137.0 (135.0–139.0)	0.47*
Potassium (mmol/L)	4.1 (4.0–4.5)	4.1 (3.9–4.35)	0.766
AST (u/L)	14.5 (11.25–20.00)	16.0 (11.0–20.0)	0.893*
ALT (u/L)	14.5 (11.25–18.00)	16.0 (11.8–20.0)	0.301*
Creatinine (mg/dl)	0.55 (0.47–0.68)	0.57 (0.47–0.68)	0.738*
Urea (mg/dl)	23.0 (17.25–30.75)	23.0 (18.0–28.0)	0.659*
PT (sec)	12.90 (12.23–15.17)	12.51 (12.13–13.50)	0.39*
INR	1.11 (1.07–1.22)	1.07 (1.02–1.14)	0.001*
PTT (sec)	24.51 (21.52–28.37)	24.80 (22.00–28.41)	0.990*
NLR	6.53 (3.81–12.78)	4.55 (2.53–8.44)	0.003*
PLR	182.41 (105.34–350.46)	138.42 (85.17–224.59)	0.008*
HALP score	3.25 (1.28–5.46)	4.43 (2.42–7.25)	0.007*
PNI	50.17 (42.85–58.21)	55.10 (47.40–60.87)	0.027*
	Complicated n (%)	Non- Complicated n (%)	
Gender			
Female	19 (39.6)	69 (33.7)	0.518**
Male	29 (60.4)	136 (63.3)	
Pathology			
Suppurative appendicitis	-	149 (72.7)	
Phlegmoneus appendicitis	-	56 (27.3)	
Gangrenous appendicitis	5 (10.4)	-	
Perforated appendicitis	41 (85.4)	-	
Plastron appendicitis	2 (4.2)	-	
*Mann Whitney U test, **Fisher exact test, MD: median, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time, INR: international normalized ratio, PTT: partial thromboplastin time, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, HALP: hemoglobin, albumin, lymphocyte, and platelet, PNI: prognostic nutritional index			

Table 2 displays the correlation analysis among the variables. A considerable positive correlation exists between NLR and PLR ($r=0.786$, $p<0.001$). NLR displayed a mild inverse association with PNI ($r=-0.698$, $p<0.001$) and a strong inverse association with HALP score ($r=-0.762$, $p<0.001$). PLR showed a strong negative association with PNI ($r=-0.788$, $p<0.001$) and a very strong negative association with HALP score ($r=-0.967$, $p<0.001$). The HALP score had a strong positive association with PNI ($r=0.875$, $p<0.001$).

Table 2. Correlations between variables								
Spearman		1	2	3	4	5	6	7
1 Appendix diameter (mm)	r	1						
	p	.						
2 CRP (mg/L)	r	.193**	1					
	p	0.002	.					
3 Na (mmol/L)	r	-.148*	-.302**	1				
	p	0.018	0.000	.				
4 INR	r	0.04	.299**	-.272**	1			
	p	0.526	0.000	0.000	.			
5 NLR	r	.222**	.230**	-.200**	.186**	1		
	p	0.000	0.000	0.001	0.003	.		
6 PLR	r	0.056	.225**	-.155*	.145*	.786**	1	
	p	0.376	0.000	0.014	0.022	0.000	.	
7 HALP	r	-0.046	-.265**	.215**	-.202**	-.762**	-.967**	1
	p	0.467	0.000	0.001	0.001	0.000	0.000	.
8 PNI	r	-0.09	-.262**	.239**	-.255**	-.698**	-.788**	.875**
	p	0.155	0.000	0.000	0.000	0.000	0.000	0.000

CRP: C-reactive protein, Na: sodium, INR: international normalized ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, HALP: hemoglobin, albumin, lymphocyte, and platelet, PNI: prognostic nutritional index, ** $p<0.01$, * $p<0.05$

DISCUSSION

Among the studies conducted so far, no prior research has specifically evaluated the prognostic value of PNI and HALP scores in pediatric appendicitis cases. In our study, we found that both the PNI ($p=0.027$) and HALP ($p=0.007$) scores were to a considerable extent lower in the CA compared to the NCA. Conversely, NLR and PLR values were to a considerable extent higher in the CA group than NCA ($p=0.003$ and $p=0.008$). Furthermore, PNI demonstrated a strong positive relationship with the HALP score, a strong negative correlation with PLR, and a moderate negative correlation with NLR. The HALP score was very strongly negatively correlated with PLR and strongly negatively correlated with NLR. Additionally, we observed a strong positive relationship between NLR and PLR.

PNI is a composite score calculated based on serum albumin and lymphocyte levels, reflecting an individual's nutritional, immunologic, and inflammatory status. Initially developed to assess prognosis and mortality risk in malnourished cancer patients (7), subsequent studies have shown its relevance in various inflammatory

processes. PNI has been found to reflect immune status, inflammation, and nutrition and has also been reported to predict overall survival in several malignancies (8,12). In a study involving 514 patients undergoing abdominal surgery, it was observed that the preoperative PNI values of patients with wound infection were markedly lower than the other patients (13). Similarly, in a study of 45 patients who underwent surgery for strangulated ileus, preoperative PNI values were significantly lower in those who developed postoperative complications compared to those who did not. Moreover, a strong negative correlation was reported between PNI and NLR (8). In another study including 699 adult patients with AcA, PNI values were markedly lower in the CA group compared to the NCA group. Regression analysis identified PNI as an important risk factor in distinguishing between CA and NCA (12). Consistent with the literature, our study found that PNI values were markedly lower in the CA cases compared to NCA ($p=0.027$). What's more, we observed a strong positive relationship between PNI and HALP score ($r=-0.875$, $p<0.001$), a strong negative correlation with PLR ($r=-0.788$, $p<0.001$), and a moderate opposite association with NLR ($r=-0.698$, $p<0.001$).

Recent studies have demonstrated that the HALP score can serve as an indicator of prognosis in various conditions involving inflammation and malignancy (9,10,14). In a retrospective study of 436 adult appendicitis cases, in the CA group, the HALP score was markedly reduced in comparison to the NCA group (15). Similarly, in another study evaluating adult AcA patients categorized by high and low HALP scores based on a cutoff value, abscess formation, perforation, and postoperative morbidity were significantly higher among those with low HALP scores (14). Consistent with these findings, our study also found a significantly lower HALP score in the CA group ($p=0.007$), along with strong negative correlations between the HALP score and both PLR ($r=-0.967$, $p<0.001$) and NLR ($r=-0.762$, $p<0.001$).

It has been widely shown that both NLR and PLR are important biomarkers reflecting systemic inflammation, not only in cancer but also in various systemic diseases (16,17). The ease with which these indices can be calculated from routine complete blood counts offers a significant practical advantage. In a study assessing inflammatory markers in adult AcA patients with CA and NCA classification, PLR and NLR were significantly elevated in the CA group, indicating their potential role in predicting CA (12). Likewise, in a study including 504 pediatric patients admitted with abdominal pain, NLR and PLR values were significantly higher among children who required surgery, suggesting these markers may serve as practical tools in identifying surgical abdominal pain in children (18). In another study involving 1265 children operated on with a prediagnosis of AcA, NLR and PLR values were found to be significantly higher in the AcA group than in the pathologically appendicitis negative group and also in the CA group than in the NCA group (19). In the course of this study, both NLR ($p=0.003$) and PLR ($p=0.008$) values were markedly elevated in the CA group, and a strong positive association was observed between these two markers ($r=0.786$, $p<0.001$). These findings may reflect increased systemic inflammation in the CA group.

Currently, imaging modalities allow for direct visualization and measurement of the appendix, and a diameter of <6 mm is generally accepted as normal, while an appendiceal diameter of ≥ 6 mm is considered a valuable diagnostic finding for appendicitis (3). In a study involving 574 adult patients diagnosed with AcA, increased appendiceal diameter on ultrasound or CT was found to be significantly associated with higher rates of CA (11). Similarly, in a study evaluating 171 pediatric cases of gangrenous and non-gangrenous appendicitis, the diameter of the appendix was considerably greater in gangrenous cases (20). In our study, we also found that the appendiceal diameter was markedly larger in the CA group ($p<0.001$). We believe that increased inflammation leads to more pronounced edema in the appendiceal wall, and the resulting obstruction of the lumen increases intraluminal pressure, contributing to this finding.

CRP is an acute phase protein, and higher CRP values have been shown to aid in the diagnosis of CA in various studies on AcA (11,21). Consistent with the literature, in our analysis, a considerable rise in CRP levels was observed in the CA ($p<0.001$).

During intense inflammatory responses, the rapid consumption of coagulation factors can lead to disseminated intravascular coagulation, a condition associated with an increased risk of bleeding (22). PT is used to assess the extrinsic hemostatic cascade, and the INR is a standardized value derived from PT that allows for consistent reporting across laboratories. Recent studies have suggested that elevated PT and INR levels may serve as predictive markers for CA (23,24). In our study, we found that both PT ($p=0.039$) and INR ($p=0.001$) levels were substantially higher in the CA group. Given the role of inflammation in surgical conditions, we recommend evaluating these parameters preoperatively to predict the severity of inflammation better and take necessary precautions.

This study has some limitations. First, its retrospective design carries the risk of information and selection bias. Second, the single-center nature of the study may limit the generalizability of the findings. Despite these limitations, the study also has some strengths. The inclusion of a relatively large cohort of patients increases the statistical power and reliability of the findings. Moreover, the combined assessment of multiple inflammatory indices such as NLR, PLR, PNI and HALP score allowed a more comprehensive analysis of the systemic inflammatory response and strengthened the robustness of prognostic assessments.

CONCLUSION

In pediatric patients, acute appendicitis is among the leading causes requiring emergency surgical intervention, and early diagnosis is crucial. In addition to routine evaluations, blood-based biomarkers derived from complete blood counts and biochemical analyses may help predict the presence of complicated appendicitis in pediatric patients presenting with abdominal pain. These biomarkers can help the surgeon select the most appropriate treatment approach.

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Ethical approval: The research was ethically approved by Aksaray University Scientific Research Ethics Committee on November 21, 2024 with decision number 2024/135.

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Exercise Tolerance Test as a Predictor of Functional Status and Surgical Outcomes in Symptomatic Spinal Stenosis Patients Undergoing Decompressive Lumbar Laminectomy

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Abstract

Aim: The aim of our study is to demonstrate the effectiveness of total laminectomy, a less invasive technique compared to fusion procedures. Additionally, we aim to evaluate preoperative and postoperative functional mobility using the treadmill exercise test.

Material and Method: This clinical study includes 16 patients who underwent their first surgery for pure spinal stenosis at the Bakırköy Mental and Neurological Diseases Hospital, Neurosurgery Clinic III. All patients underwent an exercise tolerance test using a treadmill device preoperatively and at the third postoperative month. Prior to these tests, electrocardiography and chest radiography were performed.

Results: Preoperative exercise tolerance test results indicated that initial symptoms appeared at an average of 1.42 minutes, while severe symptoms preventing test continuation emerged at an average of 6.09 minutes. At the 3-month postoperative follow-up, the exercise tolerance test results demonstrated significant improvement. The average time to the onset of initial symptoms increased to 5.39 minutes, and the onset of severe symptoms was delayed to 11.08 minutes.

Conclusion: This study demonstrates that fusionless decompression techniques remain an effective treatment option. Additionally, preoperative and postoperative treadmill exercise tests can be utilized to assess disease status and severity. Moreover, these tests serve as an objective tool for evaluating the effectiveness of surgical treatment.

Keywords: Decompressive lumbar laminectomy, surgical outcomes, exercise tolerance test

INTRODUCTION

Degenerative lumbar stenosis refers to the pathological narrowing of the lumbar canal, lateral recess, and intervertebral foramina, resulting in a reduction in their area and volume beyond a critical threshold (1). Progressive degenerative changes in the spine, including the lumbar intervertebral discs, facet joints, ligamentum flavum, and other connective tissues, are thought to play a key role in the development of lumbar stenosis over time (2-4).

The human lumbar spine segment, composed of an intervertebral disc and two facet joints, serves as a distinct and structurally complex example (5). The lower lumbar spine segments exhibit greater torsional and lateral bending movements compared to the upper lumbar segments, whereas the upper lumbar segments demonstrate more

pronounced flexion and extension movements than the lower segments, highlighting the spine's unique biomechanics (5).

Degenerative lumbar stenosis is a progressive condition that impacts all motion segments of the spine while simultaneously limiting mobility (6). Clinical symptoms include worsening leg pain during walking, increased discomfort with prolonged standing, fatigue, lower extremity discomfort, and sensory loss (4,7). Degeneration of the intervertebral discs, collapse or reduction in disc height, facet joint hypertrophy, ligamentum flavum thickening and degeneration, and calcification within the lumbar canal contribute to spinal stenosis, ultimately leading to the compression of structures such as blood vessels and nerves (2,7,8). Stenosis impairs both vascular and neural structures, hindering their ability to perform physiological functions (2,4,7).

CITATION

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Studies have shown that surgical treatments are more effective than non-surgical approaches for lumbar spinal stenosis (9). Lumbar spinal stenosis becomes more prevalent with age and is more commonly observed in women, with scientific studies reporting a prevalence ranging from 7% to 38% (2,10-13). Diagnostic evaluation involves imaging modalities and tests such as radiography, magnetic resonance imaging (MRI), computed tomography (CT), and electromyography (EMG) (2).

Non-surgical treatment options for lumbar spinal stenosis include bed rest, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, epidural steroid injections, and physical therapy (2). Severe gait disturbances affecting daily life, neurogenic claudication limiting walking to 5–10 meters, muscle weakness, rapidly progressing neurological deficits, and loss of bladder and bowel control are generally considered indications for surgical intervention.

In lumbar spinal stenosis (Figure 1), both fusion and non-fusion surgical approaches are available (14, 15). Traditional minimally invasive techniques, open surgical approaches, single-port and dual-port endoscopic techniques, fluoroscopy- and navigation-guided minimally invasive screw placement, as well as microsurgical laminectomy, microdiscectomy, and open discectomy, are employed in the surgical management of lumbar spinal stenosis (14-17).

In lumbar stenosis, clinical and physical examinations, along with walking tests and fall-related assessments, are used to evaluate both the current condition and postoperative functional status (2,18,19). Our study aims to assess the effectiveness of total laminectomy, a less invasive alternative to fusion procedures. Additionally, we aim to evaluate preoperative and postoperative functional mobility using the treadmill exercise test.

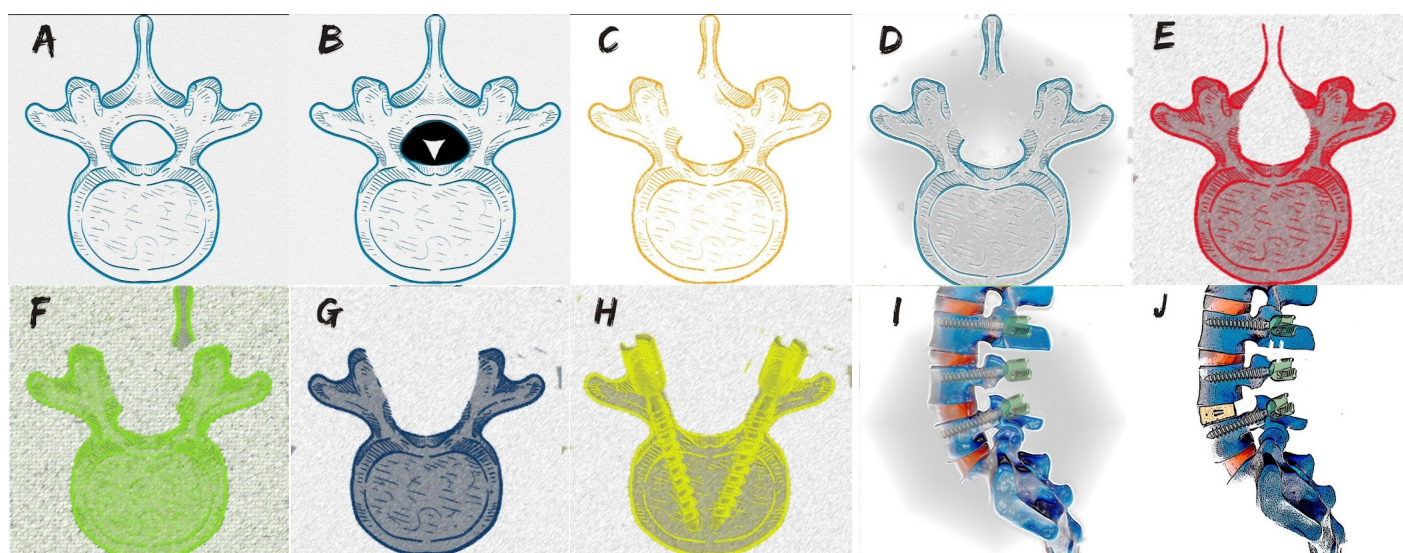


Figure 1. Illustration of lumbar decompression techniques; (A) Normal spine, (B) Spinal stenosis, (C) Unilateral laminotomy, (D) Bilateral laminotomy, (E) Split laminectomy, (F) Spinous process osteotomy, (G) Total laminectomy, (H, I, J) Fusion surgeries

MATERIAL AND METHOD

This clinical study includes 16 patients who underwent their first surgery for pure spinal stenosis at the Bakırköy Mental and Neurological Diseases Hospital, Neurosurgery Clinic III, between 1996 and 1997. The surgical procedure performed was decompressive laminectomy. All patients presented with neurogenic intermittent claudication, and radiological examinations confirmed the diagnosis of spinal stenosis. This study is a single-center, non-randomized, prospective, and observational study. Ethical approval for the present study was obtained in 1997 from the Department of Neurosurgery at Bakırköy Mental and Neurological Diseases Hospital, under the authority of Head of Department, Op. Dr. Halil Toplamaoğlu.

Preoperative and postoperative MRI examinations were conducted on all patients at the third month using a 1.5 Tesla ACSNT Philips Gyroscan MRI device. Standard imaging sequences included sagittal T1, sagittal T2, axial T2, and axial views. During these examinations, the anteroposterior

and transverse diameters of the entire lumbar canal were measured. All patients underwent the same surgical procedure, consisting of decompressive laminectomy and bilateral foraminotomy at the stenotic level.

Only patients who underwent lumbar laminectomy were included in the study. Patients who underwent instrumentation and fusion were excluded. Additionally, patients who underwent decompression for lumbar vertebral fractures were not included. Patients with severe comorbid conditions, including heart failure, were also excluded from the study.

Treadmill Test Protocol

All patients underwent an exercise tolerance test using a treadmill device preoperatively and at the third postoperative month. Prior to these tests, electrocardiography and chest radiography were performed. Additionally, internal medicine consultations were conducted to assess any contraindications for the exercise tests. These contraindications are summarized in Table 1.

Table 1. Summarize of contraindications for exercise tests	
1	Recent-onset unstable angina accompanied by chest pain
2	Untreated cardiac arrhythmias
3	Decompensated congestive heart failure
4	Advanced atrioventricular block
5	Acute myocarditis or pericarditis
6	Critical aortic stenosis
7	Severe hypertrophic obstructive cardiomyopathy
8	Uncontrolled hypertension
9	Acute systemic illnesses

The exercise tolerance test was conducted using a Morishima Exercise Equipment Motorized Treadmill at a speed of 2.8 km/h with zero incline. The test was terminated upon the emergence of severe symptoms. If the patient's symptoms were milder, the test continued for a maximum duration of 15 minutes. The speed of 2.8 km/h was selected based on previous studies, which indicated that higher speeds could induce cardiopulmonary symptoms before the onset of neurological symptoms (20).

The onset time of initial symptoms was recorded as the moment the patient first reported discomfort after starting the exercise (e.g., low back pain, leg pain, mild numbness, etc.). The onset time of severe symptoms was defined as the point at which the patient developed symptoms severe enough to prevent the continuation of the exercise test

(e.g., severe low back and leg pain, weakness, dragging of the legs, significant numbness, etc.).

Patients were instructed to maintain an upright posture on the treadmill. During the treadmill exercise test, the following data were recorded:

- Time of initial symptom onset,
- Time of severe symptom onset, preventing continuation of the test,
- Type of symptoms (e.g., low back pain, hip pain, leg pain, numbness, etc.).

For statistical analysis, the Wilcoxon signed-rank test was used to compare preoperative and postoperative results. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the 16 patients included in the study are summarized in Table 2. The cohort consisted of six males and ten females, with a mean age of 51.7 years (range: 32–64 years). The average symptom onset occurred 7.8 before surgery. During the preoperative period, all patients received medical treatment, including nonsteroidal anti-inflammatory drugs and muscle relaxants, along with bed rest. Additionally, six patients underwent physical therapy before surgery. While these interventions provided temporary symptom relief, all patients later reported recurrence.

Table 2. The treadmill test results are being monitored				
Patient	Canal diameter (mm)	Preoperative treadmill test durations (minutes)	Type of surgery	Postoperative treadmill test durations (minutes)
1	57	Initial symptom: 1:30 Severe symptom: 12	L4-L5 total laminectomy	Initial symptom: 2:30 Severe symptom: None
2	58	Initial symptom: 1:40 Severe symptom: 4:50	L3-L4 total laminectomy	Initial symptom: 4:10 Severe symptom: 11
3	60	Initial symptom: 0:30 Severe symptom: 5:10	L4-L5 total laminectomy	Initial symptom: 3:20 Severe symptom: 11:30
4	53	Initial symptom: 2:40 Severe symptom: 13	L2-L3-L4 total laminectomy	Initial symptom: 5:20 Severe symptom: None
5	78	Initial symptom: 1:30 Severe symptom: 10:15	L3-L4-L5 total laminectomy	Initial symptom: 7 Severe symptom: 13
6	63	Initial symptom: 0:25 Severe symptom: 1:30	L3-L4 total laminectomy	Initial symptom: 2:20 Severe symptom: 3:50
7	47	Initial symptom: 0:30 Severe symptom: 8:45	L5 total laminectomy	Initial symptom: 4:40 Severe symptom: None
8	88	Initial symptom: 0:50 Severe symptom: 6:15	L4-L5 total laminectomy	Initial symptom: 3:40 Severe symptom: 8:00
9	48	Initial symptom: 6:25 Severe symptom: 9:30	L3-L4-L5 total laminectomy	Initial symptom: 10:00 Severe symptom: None
10	53	Initial symptom: 0:45 Severe symptom: 3:50	L3-L4-L5 total laminectomy	Initial symptom: None Severe symptom: None
11	88	Initial symptom: 3:20 Severe symptom: 8:20	L4 total laminectomy	Initial symptom: 6:30 Severe symptom: 8:10
12	64	Initial symptom: 1:15 Severe symptom: 2:40	L3-L4 total laminectomy	Initial symptom: 3:15 Severe symptom: 9:00
13	38	Initial symptom: 0:50 Severe symptom: 2:10	L2-L3-L4-L5 total laminectomy	Initial symptom: 1:10 Severe symptom: 11:20
14	47	Initial symptom: 2:20 Severe symptom: 9:00	L5 total laminectomy	Initial symptom: 3:30 Severe symptom: 8:10
15	40	Initial symptom: 0:30 Severe symptom: 0:30	L3 total laminectomy	Initial symptom: 7:30 Severe symptom: None
16	58	Initial symptom: 2:10 Severe symptom: 6:25	L4-L5 total laminectomy	Initial symptom: 6:20 Severe symptom: None

Preoperative exercise tolerance test results indicated that initial symptoms appeared at an average of 1.42 minutes, while severe symptoms preventing test continuation emerged at an average of 6.09 minutes. At the 3-month postoperative follow-up, exercise tolerance test results demonstrated significant improvement. The average time to the onset of initial symptoms increased to 5.39 minutes, and the onset of severe symptoms was delayed to 11.08 minutes. Notably, while no patients were able to complete the maximum test duration of 15 minutes preoperatively, seven patients successfully completed the full test

postoperatively without experiencing severe symptoms. Four patients underwent decompressive laminectomy and bilateral foraminotomy at a single level, seven at two levels, four at three levels, and one at four levels. Patients were categorized by age, and their preoperative and postoperative exercise tolerance test results were analyzed (Table 3). The younger group (<49 years) demonstrated significantly better exercise tolerance both preoperatively and postoperatively compared to the older group (≥49 years) (p<0.05).

Table 3. Comparison by age groups				
Age groups	Age	Preoperative treadmill test durations (minutes)	Type of surgery	Postoperative treadmill test durations (minutes)
30–39 Age group	38	I.S: 0.45 S.S: 3.50	L3-L4-L5 total laminectomy	I.S: None S.S: None
	32	I.S: 3.20 S.S: 8.20	L4 total laminectomy	I.S: 6.30 S.S: 8.10
40–49 Age group	45	I.S: 1.30 S.S: 12	L4-L5 total laminectomy	I.S: 2.30 S.S: None
	42	I.S: 0.50 S.S: 6.15	L4-L5 total laminectomy	I.S: 3.40 S.S: 8.00
	44	I.S: 0.30 S.S: 0.30	L3 total laminectomy	I.S: 7.30 S.S: None
	41	I.S: 2.10 S.S: 6.25	L4-L5 total laminectomy	I.S: 6.20 S.S: None
50–59 Age group	55	I.S: 1.40 S.S: 4.50	L3-L4 total laminectomy	I.S: 4.10 S.S: 11.00
	54	I.S: 6.25 S.S: 9.30	L3-L4-L5 total laminectomy	I.S: 10 S.S: None
	56	I.S: 1.15 S.S: 2.40	L3-L4 total laminectomy	I.S: 3.15 S.S: 9.20
	56	I.S: 0.50 S.S: 2.10	L2-L3-L4-L5 total laminectomy	I.S: 1.10 S.S: 11.20
	52	I.S: 2.20 S.S: 9	L5 total laminectomy	I.S: 3.30 S.S: 8.10
60–69 Age group	60	I.S: 0.30 S.S: 5.10	L4-L5 total laminectomy	I.S: 3.20 S.S: 11.30
	63	I.S: 2.40 S.S: 13	L2-L3-L4 laminectomy	I.S: 5.20 S.S: None
	64	I.S: 1.30 S.S: 10.15	L3-L4-L5 total laminectomy	I.S: 7.00 S.S: 13.00
	61	I.S: 0.30 S.S: 8.45	L5 total laminectomy	I.S: 4.40 S.S: None
	63	I.S: 0.25 S.S: 1.30	L3-L4 total laminectomy	I.S: 2.20 S.S: 3.50
I.S: time of onset of initial symptoms, S.S: time of onset of severe symptoms preventing continuation of the test				

Among the eight patients with a preoperative canal diameter of <59 mm, six successfully completed the full 15-minute test postoperatively. In contrast, those with a relatively wider preoperative canal diameter (>70 mm) had less favorable exercise tolerance outcomes (Table 2).

DISCUSSION

Our study demonstrated that total laminectomy enhanced exercise tolerance test outcomes in 16 patients with lumbar spinal stenosis (Table 2, Table 3). Previous studies from the 1990s reported good to excellent surgical outcomes in 60% to 64% of patients with lumbar stenosis (21,22). Our findings align with previous research (Table 2, Table 3). In a

study by Herno et al., long-term follow-up at 7 and 13 years showed predominantly positive outcomes in patients with lumbar spinal stenosis, with unfavorable results reported in only 9.3% of cases (23). Deen et al. assessed bladder function in patients with symptomatic spinal stenosis (24). They reported improvements in bladder function tests, including increased maximum urinary flow rate and reduced post-void residual urine volume (24). Surgery is currently recommended for patients with lumbar spinal stenosis who do not respond to conservative treatment and experience reduced quality of life, paresthesia, muscle weakness, or gait disturbances (2). The primary goal is to decompress neural and vascular

structures (25). Various techniques are employed to achieve decompression, including endoscopic procedures, minimally invasive approaches, open decompression, and microscopic decompression (3, 26-28). Katz et al. reported that recovery rates were comparable between patients who underwent lumbar laminectomy alone and those who underwent lumbar decompression with fusion (3). Först et al. similarly reported that at 2- and 5-year follow-ups, clinical outcomes were comparable between the decompression-only group and the decompression-plus-fusion group (27). Our study, which demonstrated improvements in exercise tolerance test outcomes among patients who underwent laminectomy without fusion, aligns with previous literature (Table 2, Table 3). Furthermore, the decompression-plus-fusion group had higher complication rates, including increased blood loss, infection, longer hospital stays, and greater costs. (3, 27). Hermansen et al. compared minimally invasive techniques, including unilateral laminotomy with crossover, bilateral laminotomy, and spinous process osteotomy (28). The recovery outcomes of these three minimally invasive surgical techniques were found to be comparable based on the Oswestry Disability Index (28). In our patient series, traditional non-fusion total laminectomy, a less invasive approach than fusion surgeries, led to improvements in treadmill test results, a key indicator of neurogenic claudication (Tables 2 and 3). Similarly, a multicenter prospective study conducted in Switzerland found that clinical outcomes were comparable between decompression surgery with and without fusion (29). More importantly, the need for revision surgery was similar between the two groups and did not reach statistical significance (29). In surgeries for degenerative lumbar stenosis, decompression alone (Table 2, Table 3) appears to be a sufficient treatment option (27-29). Our findings, consistent with the literature (Table 2, Table 3), demonstrate improved treadmill exercise tolerance in patients who underwent laminectomy alone.

Försth et al. also assessed surgical outcomes in both groups using a walking test (27). The 6-minute walking test results for the fusion and non-fusion decompression groups were similar; however, they did not provide preoperative walking test results (27). In our study, the exercise test duration was 15 minutes. We compared preoperative and postoperative exercise test results and reported the improvement rates (Table 2, Table 3).

Deen et al. evaluated the surgical outcomes of patients with lumbar spinal stenosis using a treadmill test (30). They found that the average time to the onset of initial symptoms was 2.68 minutes, while the average time to the onset of severe symptoms was 5.47 minutes (30). In our study, preoperative exercise tolerance test results showed that the average time to the onset of initial symptoms was 1.42 minutes, while the average time to the onset of severe symptoms preventing test continuation was 6.09 minutes (Table 2, Table 3). These findings are consistent with those reported by Deen et al (30). Deen et al. reported that, after surgery, the average time to the onset of initial symptoms increased to 11.12 minutes, while the average time to the

onset of severe symptoms reached 11.81 minutes (30). In our study, postoperative (3rd month) exercise tolerance test results showed that the average time to the onset of initial symptoms was 5.39 minutes, while the average time to the onset of severe symptoms preventing test continuation was 11.08 minutes (Table 2, Table 3). When comparing our postoperative findings with those of Deen et al. (Table 2, Table 3), the time to the onset of severe symptoms after surgery appears to be comparable (30). However, a discrepancy exists between the two studies regarding the time to the onset of initial symptoms. Deen et al. reported an average of 11.12 minutes, whereas our study found a shorter duration of 5.39 minutes (Table 2, Table 3) (30). This discrepancy may be attributed to several factors, including differences in the timing of the postoperative test (Deen et al.: 2nd month; our study: 3rd month), test speed settings (Deen et al.: 1.93 km/h; our study: 2.8 km/h), surgical techniques, and patient-related factors. The treadmill test is a safe and practical tool for assessing initial functional status and objectively evaluating surgical outcomes (30, 31). Our study findings align with the literature (Table 2, Table 3). Moreover, the treadmill test demonstrates high reliability for both initial and repeat assessments (32). McIlroy et al. compared the preoperative and postoperative walking ability of patients who underwent lumbar laminectomy at up to two levels (33). They reported that patients' walking capacity continued to improve up to the 12th month following fusionless decompression surgery (33). They also stated that advanced preoperative age (>70 years), high body mass index (>35), severe leg pain, greater disability levels, and lower quality of life were associated with poorer walking ability and capacity at the 12-month follow-up (33). They also identified preoperative long walking capacity and higher education level as predictive factors for better walking capacity and walking distance at the 12-month postoperative follow-up (33). In our patient groups undergoing treadmill testing, we also observed better preoperative and postoperative outcomes in the younger group (Table 3). Our findings regarding age are consistent with those of McIlroy.

Additionally, a study conducted in Japan (which included patients who underwent fusion surgery) demonstrated that active elderly individuals who underwent spinal stenosis surgery were more capable of performing activities such as stretching and low-intensity exercises, walking, muscle-strengthening exercises, and home and garden maintenance tasks. (34). The GLFS-25 (25-Question Geriatric Locomotive Function Scale) is a tool used to assess physical pain and limitations in activities of daily living (ADL) in patients (35). The GLFS-25 test, which measures locomotive dysfunction, is a valuable tool for preoperative decision-making, assessing disease severity, and evaluating functional surgical outcomes in patients with lumbar spinal stenosis (35). An association has been identified between improvements in GLFS-25 scores and pain reduction (35). In our study, we also demonstrated an increase in exercise tolerance following surgery (Table 2, Table 3). The treadmill test used in our study can serve

as a valuable tool for preoperative decision-making and assessment, as well as for evaluating the therapeutic effects of surgery postoperatively (Table 2, Table 3). Our findings are consistent with the existing literature.

Recent studies have shown that patients who engage in appropriate postoperative exercise experience better spinal recovery compared to those who remain inactive (36). Appropriate postoperative exercises have been reported to improve pain levels, disability status, analgesic use, and psychological factors such as depression, anger, and mood disorders (37).

Endoscopic lumbar decompression is a safe and effective surgical technique for transforaminal and interlaminar procedures (38). In elderly patients for whom general anesthesia poses a risk, it is an ideal approach due to its minimal tissue damage, shorter hospital stay, and lower costs (39). The most common complication associated with endoscopic decompression is durotomy (40). This technique is not suitable for cases of pure low back pain without neurogenic symptoms, instability or deformities requiring stabilization, transforaminal decompression in the presence of central stenosis, or complex foraminal stenosis (38).

Our study has several limitations. It is based on a relatively outdated dataset, and patients' magnetic resonance imaging (MRI) scans were not recorded in the electronic database. Additionally, the sample size is small, and preoperative and postoperative quality of life or disability scores were not assessed. Due to technical limitations, certain aspects of the statistical analysis remain unclear in the preoperative and postoperative comparisons.

CONCLUSION

Our study primarily demonstrates that fusionless decompression techniques remain an effective treatment option. Additionally, preoperative and postoperative treadmill exercise tests can be utilized to assess disease status and severity before surgery. Moreover, these tests serve as an objective tool for evaluating the effectiveness of surgical treatment postoperatively.

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Clinical Course and Prognostic Factors of Isolated Pubic Ramus Fractures in Geriatric Patients

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Abstract

Aim: This study aims to evaluate the clinical outcomes of geriatric patients with pubic ramus fractures managed conservatively, assessing parameters such as length of hospitalization, blood loss, and accompanying comorbidities, and to investigate the impact of these factors on one-year mortality rates.

Material and Method: A retrospective evaluation was conducted on patients aged 65 and older diagnosed with pubic ramus fractures and admitted to a tertiary care center between 2012 and 2024. Demographic data, existing systemic diseases, laboratory findings, hospitalization duration, and mortality outcomes within a one-year follow-up were examined in detail.

Results: 60 patients were evaluated in the study, with a mean age of 78.00±7.32 years, and 71.7% of the participants were female. The mean hospitalization was calculated as 3.28±2.62 days. A statistically significant relationship was found between the burden of comorbidities and the duration of hospitalization ($p<0.001$). The change in hemoglobin data was 2.36±1.03 g/dL. The fractures of the pubic ramus were 85% unilateral. Among the comorbid conditions, heart failure was the most frequently observed, affecting 71% of the patients. Deep vein thrombosis was present in 9 patients. The mortality rate was 10 percent during the twelve-month follow-up period.

Conclusion: Isolated pubic ramus fractures in older adults should be considered a significant clinical concern due to their association with increased morbidity and mortality. Prompt identification of risk factors influencing hospitalization duration and mortality underscores the necessity of a multidisciplinary approach in patient management.

Keywords: Geriatric, pubic ramus fracture, fall-related fracture, risk factor

INTRODUCTION

With the global increase in life expectancy, fragility fractures have become a major health concern in the elderly population. Among these, isolated pubic ramus fractures are commonly observed but often underestimated in terms of their clinical impact and short-term outcomes.

Pelvic ring fractures are typically associated with high-energy trauma in younger individuals, whereas in the elderly, they more commonly result from low-energy injuries (1,2). With aging societies, the incidence of Fragility Fractures of the Pelvis (FFP), which develop especially on osteoporotic grounds, is increasing (3). One of the most common of these fractures is pubic ramus fractures (4).

In individuals over the age of 50 in the United States, pelvic fractures constitute approximately 7% of all osteoporotic fractures and are responsible for 5% of the

associated healthcare costs (5). While existing literature predominantly focuses on high-energy, unstable pelvic ring injuries in younger populations, Kannus et al. highlighted that the majority of pelvic fractures are osteoporotic reporting that 64% fall into this category, with the rate increasing to 94% among patients aged over 60 (6). Pelvic fractures in geriatric patients are injuries that are frequently associated with factors such as osteoporosis and age-related bone resorption and can lead to significant clinical and surgical difficulties. In particular, ramus pubis fractures can affect the stability of the pelvis and carry a high risk of complications, making the management of this patient group even more complex (7,8). The management of pelvic fractures in elderly patients typically necessitates a multidisciplinary approach. Treatment is individualized and tailored based on factors such as the fracture type, the patient's overall health, and any comorbid conditions present (9).

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In a study by Hamilton et al., the relationship between the duration of hospitalization and mortality in geriatric patients with ramus pubis fractures was examined and it was found that these fractures increased mortality, especially in combination with comorbid conditions such as cardiovascular diseases (10). This study reveals that mortality rates associated with ramus pubis fractures in geriatric patients vary according to age, comorbidity status, and response to treatment. Pubic ramus fractures are frequently associated with skeletal problems such as osteoporosis in geriatric patients, which may further complicate the treatment process. Comorbidities, especially cardiovascular and metabolic diseases, are important factors determining treatment outcomes (7,8,11). Furthermore, due to the high risk of falls in geriatric individuals, early diagnosis and appropriate treatment of these fractures are of vital importance (12).

MATERIAL AND METHOD

This study retrospectively examines the clinical outcomes of pubic ramus fractures in elderly patients. A total of 60 geriatric patients, diagnosed with pubic ramus fractures, were included from those admitted to the Emergency Department of the Department of Orthopaedics and Traumatology at Düzce University between 2012 and 2024. Approval for the study was obtained from the Düzce University Non-Interventional Clinical Research Ethics Committee (Date: 21.04.2025 number: 2024/115). By ethical guidelines, patient data were anonymized and analyzed in adherence to confidentiality protocols. The study included only patients diagnosed with isolated pubic ramus fractures who were treated conservatively and followed for a minimum of one year. Patients with posterior pelvic, acetabulum, and lower extremity long bone fractures, patients who had undergone pelvic surgery, Patients who experienced severe trauma unrelated to the fracture, and those with concurrent terminal illnesses were excluded from the study.

The data were retrieved from the hospital's archive. The parameters analyzed included demographic information (age, gender,) existing comorbidities (Diabetes, Heart failure, Respiratory failure, Cognitive disease, Osteoporosis, Coagulopathy), type of fracture (unilateral or bilateral), duration of hospitalization, changes in hemoglobin levels, need for blood transfusion and mortality at 1-year follow-up.

The first imaging method was anteroposterior (AP) X-ray evaluation. In patients in whom the pelvic ring could not be evaluated, the diagnosis was made with the help of Computed Tomography (CT). When the decrease in the control hemoglobin value of the hospitalized patients stopped, the absence of additional symptoms that would prevent discharge (cardiac or respiratory failure) and the time until discharge were accepted as the duration of hospitalization. The follow-up of the patients after discharge was completed for 1 year with X-ray radiograph controls at 2-week intervals for 6 weeks, 1 month after mobilization started in the sixth week, and then at 3-month intervals. Until the end of the 6-week absolute bed rest and immobilization period, antiembolic treatment was applied to the patients.

Pain management, early mobilization, and physical therapy applications formed the basis of the treatment process. Patients were evaluated clinically and radiologically at regular intervals during follow-up. In clinical follow-up, pain levels, mobility, healing time, and level of independence were taken into consideration. In radiological follow-up, pelvic X-ray radiographs and CT imaging were used when necessary, and fracture healing processes were monitored.

Statistical Analyses

For continuous data, descriptive statistics were calculated using the mean±standard deviation, median, and range (minimum-maximum), while categorical variables were reported as frequencies and percentages. The Shapiro-Wilk test was used to test for normality in continuous data. Comparisons between two groups for continuous variables were performed using the Mann-Whitney U test. For categorical variables, Chi-Square and Fisher's Exact tests were applied where appropriate. All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL), with a significance level set at p<0.05.

RESULTS

The study included 60 patients. The mean age of the patients was 78.00±7.32 years, with a minimum age of 65 years and a maximum age of 94 years. Of the patients, 71.87% were female, 15% had bilateral fractures, and 60% had a single fracture. The demographic characteristics of the patients are summarized in Table 1. The prevalence of diabetes was 68.3%, heart failure was 71.7%, respiratory failure was 41.7%, cognitive disorders were present in 43.3%, osteoporosis in 68.3%, and coagulopathy in 60%. Deep vein thrombosis was observed in 15% of the patients. The distribution of comorbidities of the patients are given in Figure 1. During the one-year follow-up, 10% of the patients died.

Table 1. Characteristics of the patients		
	Mean±SD	Median (Min-Max)
Age (years)	78.00±7.32	79 (65-94)
Haemoglobin change	2.36±1.03	1.9 (1.2-1.4)
Amount of Blood used (unit)	1.25±1.14	1 (0-5)
Hospitalization days	3.28±2.62	2 (1-15)
	n	%
Gender		
Right	43	71.7
Male	17	28.3
Side		
Right	23	38.3
Left	28	46.7
Bilateral	9	15.0
Broken bone (Superior-inferior ramus)		
1	36	60
2	21	35
3	3	5.0

SD: standard deviation

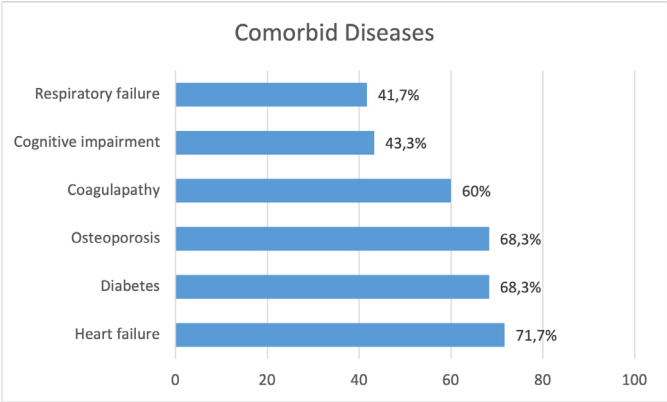


Figure 1. Rates of comorbidities in patients

Patients with coagulopathy had a higher decrease in hemoglobin (2.36 ± 1.03), greater blood transfusion

needs (1.25 ± 1.14), and longer hospitalization durations (3.28 ± 2.62 days) compared to those without coagulopathy ($p<0.001$). There was no significant difference in hospitalization durations between patients with and without diabetes ($p>0.05$) (Table 2). Patients with heart failure had longer hospitalization periods ($p<0.01$). No significant difference was found in the hospitalization durations between patients with respiratory failure and those without cognitive disorders ($p>0.05$). Patients with osteoporosis had longer hospitalization durations ($p<0.01$). Patients with deep vein thrombosis also had longer hospitalization periods ($p<0.05$). Hospitalization duration comparisons in comorbidities are given in Table 3.

No significant difference was observed in the mortality rates between patients with and without coagulopathy ($p>0.05$).

Table 2. Comparison of haemoglobin change, blood volume and length of hospitalization between patients without coagulopathy and patients with coagulopathy

	Coagulopathy (-) (n=24)		Coagulopathy (+) (n=36)		p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Hemoglobin decline	1.72±0.48	1.5 (1.2-3.3)	2.79±1.08	2.8 (1.2-4.8)	<0.001 ^b
Blood used (units)	0.42±0.58	0 (0-2)	1.18±1.09	2 (0-5)	<0.001 ^b
Hospitalization days	1.91±1.01	2 (1-5)	4.19±2.96	3 (1-15)	<0.001 ^b

b: Mann Whitney U test, SD: standard deviation

Table 3. Hospitalization duration comparisons in comorbidities

		Hospitalization days		
	n	Mean±SD	Median (Min-Max)	p
Diabetes				
None	19	3.84±2.40	3 (1-10)	0.079 ^b
Yes	41	3.02±2.70	2 (1-15)	
Heart failure				
None	17	1.88±1.11	2 (1-5)	0.001 ^b
Yes	43	3.83±1.84	3 (1-15)	
Respiratory failure				
None	35	3.34±2.79	3 (1-15)	0.982 ^b
Yes	25	3.20±2.41	2 (1-10)	
Cognitive impairment				
None	34	3.32±2.33	3 (1-10)	0.497 ^b
Yes	26	3.23±3.01	2 (1-15)	
Osteoporosis				
None	19	1.89±1.10	2 (1-5)	0.001 ^b
Yes	41	3.92±2.87	3 (1-15)	
Coagulopathy				
None	24	1.91±1.01	2 (1-5)	<0.001 ^b
Yes	36	4.19±2.96	3 (1-15)	

b: Mann Whitney U test, SD: standard deviation

DISCUSSION

In this study, we evaluated the comorbidity profile, hematological parameters, blood transfusion requirement, length of hospitalization and one-year mortality rates of isolated pubic ramus fractures followed conservatively in the geriatric age group.

In elderly individuals, these pubic ramus fractures often occur with low-energy traumas and treatment management is directly related to the patient's general condition, comorbidities, and fracture type (5,13). Therefore, conservative treatment is generally preferred, but the healing process may be prolonged with age (4,5,9). In this

study, according to the literature, all 60 patients with isolated pubic ramus fractures without any additional fractures had a history of fracture after a simple fall or low-energy trauma.

The effect of comorbid diseases on the conservative treatment of pubic ramus fractures is quite evident (5,8). Especially the presence of dementia, Alzheimer's disease, Chronic obstructive pulmonary disease (COPD), and cardiovascular diseases increases the risk of complications by making compliance with treatment and mobilization difficult (8,9,14). Therefore, a multidisciplinary approach is inevitable in these fractures. Integration of geriatrics, internal medicine, neurology, cardiology, and pulmonology specialists into the process may positively affect the response of patients to treatment (15). In our study, cognitive disorders, along with diseases of the cardiac and respiratory systems, were found to be prevalent in the majority of patients, consistent with existing literature. As in previous studies, a collaborative approach involving relevant specialties was adopted for the treatment planning of all patients, beginning at hospitalization and continuing after discharge.

Osteoporosis constitutes a significant risk factor for pelvic fractures, and the majority of these fractures in individuals aged over 60 are attributed to osteoporotic causes (16). Kanis et al. reported that approximately 7% of osteoporotic fractures affect the pelvic ring and 94% of pelvic fractures are associated with osteoporosis (17). However, this rate was found to be 68.3% in our study, which is lower than the literature. This difference may be because osteoporosis screening has not yet become routine in patients diagnosed with pubic ramus fracture or in geriatric age groups treated for any fracture in our country.

Cognitive disorders, including dementia, are significant contributors to the increased risk of falls in older adults. In these patients, factors such as attention deficits, disorientation, and postural instability heighten their vulnerability to low-energy trauma (18). Tsutsumimoto et al. reported that there are delays in the diagnosis of pubic ramus fractures in individuals with dementia and posterior pelvic ring injuries are often missed. In addition, these patients have difficulty expressing their pain, leading to delayed mobilization and increased complications (19). In our study, when the patient anamnesis was carefully analyzed, there was no clear information about the mechanism and time of simple trauma in geriatric patients living alone. Therefore, it is important to consider the cognitive status in the initial evaluation of geriatric patients with pubic ramus fracture.

Cardiopulmonary diseases such as cardiac and respiratory failure are among the factors that directly affect the recovery process (14,20). These conditions increase postoperative complication rates, prolong hospitalization, and decrease functional independence (16,21,22). Although no direct correlation was observed between the length of hospitalization in our patients with respiratory failure, the length of hospitalization was found to be higher in our patients with heart failure. In addition, patients with osteoporosis, coagulopathy, and deep vein thrombosis had statistically longer hospitalization. In patients with this pubic

ramus fracture, meticulous monitoring of oxygenation and cardiac performance and regulation of coagulopathy are critical for a successful treatment process.

The review published by Roßler et al. in 2024, in which they analyzed the studies after 2000, reveals that the number of cases with mortality in ramus pubic fractures due to low-energy trauma is relatively low (23). However, the increase in the amount of hemorrhage revealed in our study may cause an increase in morbidity and mortality.

The number of concomitant comorbid diseases and especially the presence of coagulopathy increases the amount of bleeding at the fracture site in pubic ramus fractures and this affects the hemoglobin value (24). In our study, the presence of coagulopathy resulted in more bleeding and associated hemoglobin decrease (2.79 ± 1.08 g/dL), more blood product use (1.18 ± 1.09 units), and increased hospitalization (4.19 ± 2.96) days ($p < 0.001$). Unlike other comorbid diseases, this negative effect of coagulopathy is an important parameter in the evaluation of morbidity in geriatric patients with pubic ramus fracture.

This study has some limitations. Firstly, since the study was conducted retrospectively, patient information was analyzed through the existing file records. This may cause some data to be missing or inadequate. Secondly, since the patients included in the study were not routinely screened for osteoporosis, data on bone health were limited. This made it difficult to fully assess the effect of osteoporosis on fracture occurrence. In addition, the cognitive status of the patients was assessed based on available medical records, not on detailed tests. This made it difficult to determine the severity of conditions such as dementia. Another limitation is that the causes of death were not analyzed in detail. Therefore, it was not possible to determine whether mortality was related to fracture or other comorbidities. Finally, the fact that the study was conducted in a single centre and with a limited number of patients limits the generalizability of the results. Larger and multicentre studies are needed to understand this issue more clearly.

CONCLUSION

Conservative treatment is a safe option in geriatric patients with isolated pubic ramus fractures due to simple trauma. However, the success of this process is closely related to the patient's general health status, comorbidities, and hematological values. Therefore, individualized and interdisciplinary approaches are indispensable for optimal clinical outcomes in geriatric patients.

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From Safety to Risk: Maternal Morbidity in Women Undergoing Multiple Repeat Cesarean Deliveries

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Abstract

Aim: The global rise in cesarean delivery (CD) rates, especially in low- and middle-income countries, has increased the prevalence of multiple repeat cesarean deliveries (MRCs), raising concerns about associated maternal and neonatal morbidity. The objective of this study was to assess clinical outcomes related to MRCs by comparing women with four or more prior CDs to those with fewer.

Material and Method: This study was retrospectively conducted involving 15,811 women with singleton pregnancies who underwent CD and had a history of at least one prior CD between January 2018 and December 2022. Participants were categorized into two groups: Group 1 (≤ 3 prior CDs) and Group 2 (≥ 4 prior CDs). Maternal demographics, intraoperative and postoperative outcomes, as well as neonatal outcomes, were analyzed and evaluated across the groups.

Results: Women in Group 2 had significantly higher rates of placenta previa (7.4% vs. 0.23%), placenta accreta (1.9% vs. 0.04%), cesarean hysterectomy (1.5% vs. 0.007%), intra-abdominal adhesion (7.3% vs. 1.21%), bladder injury (1.06% vs. 0.095%), and blood transfusion (8.7% vs. 2.6%) than those in Group 1 (all $p < 0.001$). Neonatal outcomes were also adversely affected in Group 2, with lower gestational age at delivery (37.6 vs. 38.4 weeks) and increased NICU admission rate (10.2% vs. 7.6%; $p < 0.001$).

Conclusion: MRCs are significantly associated with increased maternal and neonatal morbidity, particularly in women with four or more previous CDs. These findings emphasize the need for comprehensive prenatal counseling, surgical preparedness, and efforts to reduce primary CD rates, while promoting trial of labor after CD when clinically appropriate.

Keywords: Cesarean delivery, maternal, multiple repeat, neonatal, outcomes

INTRODUCTION

Cesarean delivery (CD) is an essential and frequently performed obstetric surgical procedure used to address complications of vaginal delivery, such as cephalopelvic disproportion, fetal distress, obstetric hemorrhage, abnormal presentation, and other emergent conditions, effectively serving as a critical intervention to safeguard maternal and neonatal health. While, as a surgical procedure, CD entails inherent risks, including anesthetic complications, infection, bleeding, thromboembolism, and surgical injury (1). Compared with primary CD, multiple repeat cesarean deliveries (MRCs) are associated with increased risks, including dense adhesion, bladder and bowel injury, placenta previa (PP), intensive care unit (ICU) admission and placenta accreta (PA) (2). Additionally, neonates delivered via CD are at an increased risk for infection, respiratory complications, and admission to the neonatal intensive care unit (NICU) (3).

The global incidence of CD has increased significantly in recent decades, driven by multiple factors, including changes in maternal characteristics, evolving professional practice patterns, medico-legal considerations, socio-economic and cultural influences, and the growing utilization of assisted reproductive technologies (4). Based on 2021 data from the OECD in 2021, Israel recorded the lowest rate of CDs among its member countries at 148 per 1,000 live births, however Mexico had the highest rate at 586, closely followed by Türkiye, which had the second highest rate at 573 per 1,000 live births (5). In addition, findings from the Türkiye Demographic and Health Survey indicate a significant increase in Türkiye's CD rate, from 8% in 1993 to 37% in 2008 and further to 52% in 2018, reflecting a significant upward trend over a 25-year period (6-8). Nevertheless, in 1985, the World Health Organization stated that the optimal CD rate at the population level should be between 10% and 15%, as rates above this threshold are not associated with additional reductions in maternal or perinatal mortality (9).

CITATION

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The increasing incidence of CD in developing countries has led to a growing number of women undergoing MRCs. Vaginal birth after CD represents a viable strategy to reduce CD rates; however, it is not routinely offered in all hospitals in Türkiye. Moreover, many clinicians recommend sterilization to women after two or three CD because of the risk of uterine rupture, postpartum hemorrhage and other complications. However, sterilization is frequently declined by women in Türkiye, where large families are socially and culturally encouraged.

The maximum number of CDs that a woman can safely undergo remains a subject of ongoing debate. Therefore, the primary objective of this study was to assess the safety of MRCs and establish the maximum number that can be performed without significantly increasing maternal or neonatal risk. In addition, the study aimed to compare operative outcomes, clinical findings, maternal morbidity, and neonatal outcomes between women with a history of four or more CDs and those with three or fewer.

MATERIAL AND METHOD

This retrospective case-control study was conducted in the Department of Perinatology at a tertiary care center between January 2018 and December 2022, involving women aged 20 to 45 years with singleton pregnancies and a history of at least one prior CD. Participants with multiple gestations were excluded, as multiple pregnancies are a well-established primary risk factor for both maternal and neonatal morbidity. This study was carried out in compliance with the ethical standards of the Declaration of Helsinki and was approved by the institutional ethics committee of University of Health Sciences Etlik Zübeyde Hanım Health Care Training and Research Hospital (Date: 20.05.2021, Reference Number: 07/10).

Clinical data were obtained from electronic patient records and included maternal age, parity, maternal body mass index, antenatal follow-up, operative time, intraoperative and postoperative complications, PP, PA, need for hysterectomy, blood transfusion, admission to ICU, length of hospital stay and incidence of bladder and bowel injury and wound infection. Neonatal data collected included gestational age, birth weight, Apgar scores <7 at 5 minutes, and admission to NICU. Patients were divided into two groups based on the number of their prior CDs. Group 1 included women with three or fewer prior CDs, while Group 2 included those with four or more.

All patients underwent abdominal ultrasound and, when clinically indicated, transvaginal ultrasound with color Doppler imaging, performed using a Voluson E6 device (GE Healthcare, Milwaukee, WI, USA). Gestational age was estimated using the date of the last menstrual period and verified through an ultrasound examination. If PP was suspected during routine ultrasound examination, the diagnosis was established by transvaginal ultrasound at 32 weeks' gestation, defined as complete coverage of the cervical os or a placental edge within 20 mm of the os (10). The diagnosis was confirmed by a repeat transabdominal or transvaginal ultrasound examination performed between 32 and 34 weeks' gestation. The diagnosis of PA was made according to the ultrasound criteria defined by the European

Working Group on Abnormally Invasive Placenta (11). The definitive diagnosis of PA was confirmed by clinical evidence of placental invasion observed during delivery or by histopathological examination of hysterectomy specimens, in accordance with the International Federation of Gynecology and Obstetrics guidelines (12). If PA was suspected, the standard practice was to anticipate the condition, counsel the patient about potential complications and the possible need for blood transfusion, and obtain informed consent for hysterectomy.

Scar dehiscence was defined as the separation of a previous cesarean scar while the overlying peritoneum remains intact. Uterine rupture was characterized by a complete, full-thickness tear of a prior cesarean scar, typically associated with partial or total displacement of the fetus into the abdominal cavity. Adhesions involving the anterior uterine wall and peritoneum, the omentum, and the bladder were documented. Intraoperative visceral injuries were defined as unintentional damage sustained during a surgical incision or tissue dissection, including bladder and bowel injuries, such as accidental intussusception into the intestine or seromuscular damage that required surgical repair. Wound infection was diagnosed when the CD incision exhibited drainage of serosanguinous or purulent fluid accompanied by induration and tenderness. Estimated blood loss was calculated by summing the volume collected in the suction canister and the weight difference between dry and blood-soaked gauze and surgical towels, assuming that 1 g equals 1 mL. Blood transfusion was indicated in cases where the preoperative hemoglobin (Hb) level was below 10 g/dL, intraoperative estimated blood loss exceeded 20% of the total blood volume, or the postoperative Hb level was below 8.5 g/dL. In accordance with the criteria set by the Turkish Ministry of Health, a minimum of four antenatal visits was considered indicative of regular antenatal care.

Data Analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±standard deviation (SD) for normally distributed data or as median values for non-normally distributed data, while categorical variables were expressed as percentages. Comparisons between the two groups for normally distributed variables were performed using the independent samples t-test. The Mann-Whitney U test was applied to variables without normal distribution. The Pearson chi-square test was used to compare categorical variables.

RESULTS

Over the study period, 56,854 deliveries occurred at our hospital, of which 15,811 (27.8%) were CDs. The sociodemographic and clinical characteristics of the study population are presented in Table 1. Of the CDs, 6,702 (42.4%) were primary CDs, whereas 9,109 (57.6%) were performed in women with at least one prior CD. More than half of the participants (51.6%) were under 30 years of age. The majority of participants were of Turkish nationality (81%), followed by Syrian nationals (15.9%) and individuals from other nationalities (3.1%). Moreover, 81% received regular antenatal care, and only 3% reported smoking during pregnancy.

Table 1. Demographic and clinical features of the study population

Variables		Number	Percentage
Maternal age (years, mean±SD)	<30	8158	51.6
	30–35	4727	29.9
	>35	2926	18.5
Parity (n, %)	1	6702	42.4
	2	4111	25.8
	3	2830	17.9
	4	1582	10.2
	≥5	586	3.7
Number of previous cesarean deliveries (n, %)	1	6702	42.4
	2	4111	25.8
	3	2830	17.9
	≥4	2168	13.9
Nationality (n, %)	Turkish	12809	81
	Syrian	2510	15.9
	Others	492	3.1
BMI (kg/m², n, %)	<25	21500	52
	25–30	14500	35.1
	>30	5352	12.9
Had regular antenatal care	Yes	13441	85
	No	2370	15
Smoking (during pregnancy)	Yes	475	3
	No	15336	97

BMI: body mass index, SD: standard deviation

As shown in Figure 1, the most frequent indication for CD among patients undergoing a primary CD was failure to progress, accounting for 59.5% of cases. This was followed by breech presentation (12.5%), fetal distress (11.0%), and intrauterine growth restriction (8.6%). In patients with MRCDs, the most commonly reported indication was a previous CD, also comprising 59.5% of cases, as illustrated in Figure 2. Other reported indications in this group included breech presentation (4.5%), fetal distress (3.7%), oligohydramnios (3.5%), preeclampsia (2.9%), and transverse lie (0.2%).

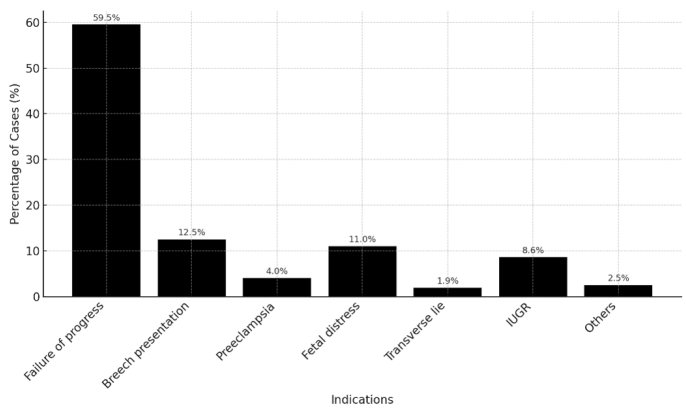


Figure 1. Distribution of indications for primary cesarean delivery

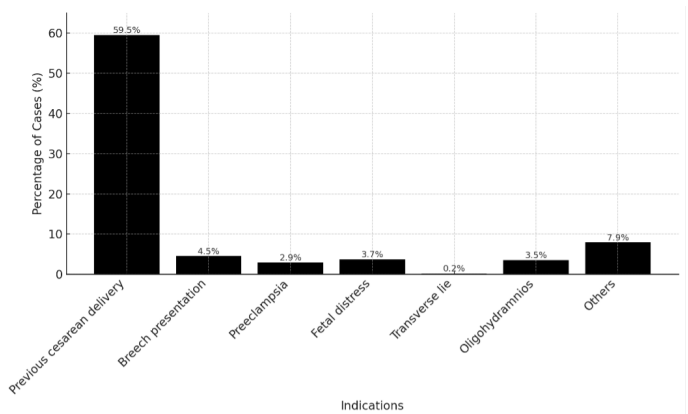


Figure 2. Distribution of indications for multiple repeat cesarean deliveries

As shown in Table 2, Group 1 included 13,643 patients (86.3%), while Group 2 included 2,168 patients (13.7%). Women in Group 2 were significantly older and had higher parity than those in Group 1 (both $p<0.001$). Additionally, the prevalence of gestational diabetes mellitus (24.6% vs. 15.2%; $p<0.001$) and the rate of pregnancy-induced hypertension or preeclampsia was higher (8.9% vs. 11.8%; $p=0.002$) in Group 2. Preoperative and postoperative hemoglobin levels did not differ significantly between the groups.

Table 2. Demographic and clinical characteristics between the groups

	Group 1 (number of CDs ≤3, n=13643)	Group 2 (number of CDs ≥4, n=2168)	p-value
Maternal age (years, mean±SD)	27.78±6.93 (18-39)	34.93±2.90 (24-45)	<0.001
Parity (mean±SD)	2.63±1.29 (1-4)	3.52±1.42 (3-7)	<0.001
Preop Hb (g/dL, mean±SD)	10.1±1.4	10.2±0.8	0.264
Postop Hb (g/dL, mean±SD)	10±1.2	9.5±1.1	0.052
Medical problems (n, %)			
Pregestational diabetes	615 (4.51)	106 (4.90)	0.0639
Gestational diabetes mellitus	2074 (15.2)	533 (24.6)	<0.001
PIH/preeclampsia	1214 (8.9)	256 (11.8)	0.002
Anemia	314 (2.3)	54 (2.5)	0.585
Hypothyroidism	368 (2.7)	63 (2.9)	0.756

PIH: pregnancy induced hypertension, SD: standard deviation

As shown in Table 3, intraoperative outcomes were compared between the participants in Group 1 and Group 2. The operative time was significantly longer in Group 2 (68.42 vs. 54.35 minutes), with greater estimated blood loss (1015.4 vs. 605.3 mL) and longer hospital stay (4.7 vs. 3.3 days) than those Group 1 (all p<0.001). The incidence of midline abdominal incision (6.1% vs. 1.7%), PP (7.4% vs. 0.23%),

cesarean hysterectomy (1.5% vs. 0.007%), intra-abdominal dense adhesions (7.3% vs. 1.21%) and blood transfusion (8.7% vs. 2.6%) were all significantly higher in Group 2 (all p<0.001). Additionally, uterine scar dehiscence or rupture (0.14% vs. 0.007%), bowel injury (0.046% vs. 0%), wound infection (0.322% vs. 0.088%), and admission to ICU (0.14% vs. 0.007%) were more common in Group 2 (all p<0.001).

Table 3. Comparison of intraoperative outcomes between groups

Variables	Group 1 (n=13643)	Group 2 (n=2168)	p-value
Operative time (minutes, mean±SD)	54.35±15.4	68.42±18.5	<0.001
Type of abdominal incision (n, %)			
Midline	232 (1.7)	132 (6.1)	<0.001
Pfannenstiel	13411 (98.3)	2036 (93.9)	
Length of hospital stay (days, mean±SD)	3.3±0.5	4.7±0.3	<0.001
Estimated blood loss (mL, mean±SD)	605.3±150.5	1015.4±175.4	<0.001
Blood transfusion (n, %)	355 (2.6)	189 (8.7)	<0.001
Plasenta previa (n, %)	31 (0.23)	160 (7.4)	<0.001
Placenta accreta (n, %)	5 (0.04)	41 (1.9)	<0.001
Cesarean Hysterectomy (n, %)	1 (0.007)	32 (1.5)	<0.001
Uterine scar dehiscence or rupture (n, %)	1 (0.007)	3 (0.14)	<0.001
Intra-abdominal dense adhesion (n, %)	165 (1.21)	158 (7.3)	<0.001
Bladder injury (n, %)	13 (0.095)	23 (1.06)	<0.001
Bowel injury (n, %)	0	1 (0.046)	<0.001
Wound infection (n, %)	12 (0.088)	7 (0.322)	<0.001
ICU admission (n, %)	1 (0.007)	3 (0.14)	<0.001

ICU: intensive care unit, SD: standard deviation

Neonatal outcomes were compared between patients in Group 1 and Group 2 are shown in Table 4. Gestational age at delivery was significantly lower in Group 2 (37.6±0.2 vs. 38.4±1.8 weeks; p<0.001). The

rate of preterm delivery before 37 weeks (2.3% vs. 0.2%) and NICU admission rates (10.2% vs. 7.6%) were significantly higher in Group 2 than those in Group 1 (both p<0.001).

Table 4. Neonatal characteristics and neonatal outcome

Variables	Group 1 (n=13643)	Group 2 (n=2168)	p-value
Gestational age (weeks, mean±SD)	38.4±1.8	37.6±0.2	<0.001
Birth weight (grams, mean±SD)	3149±468	3089±238	0.256
Apgar score ≤7 at 5 minutes (n, %)	109 (0.8)	22 (1)	0.581
5. minutes Apgar score (mean±SD)	7.4±1.3	7.5±1.4	0.0152
Delivery at <37 weeks (n, %)	26 (0.2)	5 (2.3)	<0.001
NICU admission (n, %)	1037 (7.6)	221 (10.2)	<0.001

NICU: neonatal intensive care unit, SD: standard deviation

DISCUSSION

The increasing global prevalence of CDs, particularly in low- and middle-income countries, has raised significant concerns regarding the short- and long-term consequences of MRCDs (2-3). Although primary CD can be vital for ensuring the well-being of women and their offspring in specific obstetric situations, the growing trend towards repeat procedures, often influenced by a history of prior CD rather than new medical indications, poses substantial clinical, surgical, and public health challenges.

Cultural expectations favoring larger families, prevalent in many regions globally, particularly within Arabian and Turkish communities, have contributed to a rise in CD rates and, consequently to an increase in MRCDs and their related complications. To provide accurate counseling on the safety of MRCDs, numerous studies have been conducted to investigate the risks and outcomes associated with these procedures.

One of the most critical complications associated with MRCDs is abnormal placentation, particularly PP and PA. Marshall et al. reported that the risk of PP is 1% with one previous CD, while this risk increases to 2.8% with three or more (13). Similarly, Makoha et al. reported that the risk of PP, PA and caesarean hysterectomy were substantially increased with the fifth and sixth CD compared with the third CD (14). Consistent with previous findings, the study observed a significantly higher rate of PP among women with four or more previous CDs than among those with fewer (7.4% vs. 0.23%), along with an increased rate of PA (1.9% vs. 0.04%). Similarly, Jauniaux et al. reported that the rate of PA increased from 4.1% in women with one previous CD to 13.3% in those with two or more (15). Likewise, Silver et al. identified a dose-dependent relationship, noting that the risk of PP increased from 0.9% after one CD to 3.4% after four or more. They also found that even in the absence of PP or PA, the risk of cesarean hysterectomy increased with the number of previous CDs (16). Consequently, a major cause of emergency cesarean hysterectomy is massive bleeding due to abnormal placental invasion. Consistent with this, this study found increased estimated blood loss (1015.4 vs 605.3 mL) and a significantly higher rate of cesarean hysterectomy in Group 2 compared with Group 1 (1.5% vs. 0.007%).

Tulandi et al. reported that adhesions form in up to 90% of patients following multiple abdominal surgeries, creating dense fibrotic bands that complicate dissection and increase the risk of iatrogenic injury (17). Furthermore, the literature demonstrates a progressive increase in the incidence of intraperitoneal adhesions with the number of prior CDs. Reported adhesion rates range from 12% to 46% in patients with two prior CDs and from 26% to 75% in those with three prior CDs (17,18). Rashid et al. found that the adhesion rate in patients with five or more prior CDs was 54%, compared with 15% in a control group with two to three prior CDs (19). Similarly, Kaplanoglu et al. reported an adhesion rate of 19.4% in women with three or fewer prior CDs, rising to 58.6% in those with four or more prior CDs, suggesting that the fourth CD may represent a critical threshold for adhesion formation (20). The presence of adhesions is known to complicate subsequent abdominal surgery, leading to prolonged operative times, an increased need for blood transfusion, and a higher risk of injury to adjacent structures, such as bowel, ureter and bladder (17-19). Consistent with these observations, our study demonstrated significant technical challenges in women with MRCDs, with Group 2 exhibiting higher rates of intraabdominal dense adhesions (7.3% vs. 1.21%), bladder injury (1.06% vs. 0.095%), and blood transfusion (8.7% vs. 2.6%) compared with Group 1. Bladder injury is an uncommon but well-recognized complication of MRCDs, particularly among women with previous low transverse incisions, owing to adhesions between the bladder and the anterior uterine wall (21). These findings reflect the cumulative effect of repeated surgical trauma on pelvic anatomy, as observed in our cohort of 15,811 cesarean deliveries.

Another significant complication associated with MRCDs was the increased risk of uterine scar dehiscence or rupture, which contributes to increased maternal and offspring morbidity and mortality. The study confirmed that the prevalence of uterine scar dehiscence and rupture increased with the number of previous CDs, as evidenced by the higher rate observed in Group 2. These results align with the findings of Uygur et al. (18) and Qublan et al. (22), who likewise reported a heightened risk of uterine scar complications associated with MRCDs. Conversely, studies by Macones et al. (23) and Cahill et al. (24) found no significant association between an increased number

of prior CDs and the incidence of uterine scar rupture, underscoring the variability of outcomes among different study populations.

Group 2 had poorer neonatal outcomes, as evidenced by a lower gestational age at delivery and a higher NICU admission rate compared to Group 1. Similarly, Oben et al. reported an increased rate of neonatal morbidity associated with preterm birth in women with MRCDs (25). In contrast, Uygur et al. (18) and Rashid et al. (19) reported no statistically significant differences in Apgar scores or NICU admission rates among neonates born to mothers with varying numbers of prior CDs. The earlier gestational age in Group 2 may be due to the higher incidence of PP and PA, which often require planned preterm delivery to prevent catastrophic hemorrhage.

Our study has certain limitations that should be acknowledged. Firstly, its retrospective nature limits the possibility of establishing cause-effect and may introduce information and selection bias. Secondly, being conducted at a single tertiary care facility, the results may not be applicable to a wide range of settings with varying patient demographics, clinical practices, or healthcare infrastructures. Thirdly, despite the fact that comprehensive data were retrieved from the hospital's digital medical database, we cannot exclude possibility that some variables were not fully documented. Consequently, detailed operative notes, adhesion grading, and estimated blood loss relied on subjective surgical descriptions, limiting their objective assessment in this retrospective analysis. Despite the aforementioned limitations, the extensive sample size and the study's focus on objective clinical outcomes support the reliability and relevance of the results.

CONCLUSION

This study demonstrates that MRCDs are significantly associated with increased maternal and offspring morbidity, particularly in women with four or more previous CDs. These findings highlight the importance of individualized care planning, multidisciplinary surgical preparedness, and comprehensive patient counseling. Efforts to reduce primary CD rates and promote trial of labor after CD, where clinically appropriate, are essential to reduce the long-term risks associated with MRCD.

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Anemia in the Elderly Receiving Home Healthcare Service: Association with Their Functional

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Abstract

Aim: Anemia is an important health problem that is common in the elderly and results in a decline in quality of life and a rise in mortality and morbidity. This study aims to evaluate anemia prevalence in elderly individuals who are characterized in many respects and who receive home healthcare service and the relationship between the anemia index for activities of daily living and nutritional status.

Material and Method: Our retrospective, cross-sectional and descriptive study consisted of patients above the age of 65 receiving home healthcare services. Demographic information, presence of a chronic disease, nutritional status and Barthel Index for Basic Daily Living Activities of the patients followed up between October 2023 and March 2024 were recorded. Anemia was diagnosed in accordance with the criteria of the World Health Organization (WHO) as the serum hemoglobin level was under 13 g/dL in male patients and 12 g/dL in female patients. $p < 0.05$ was considered statistically significant.

Results: There were a total of 593 people involved in the study. Of the participants in the study, 358 (60.4%) were female. Mean age was 81.1 ± 8.0 years. Mean hemoglobin level was 11.8 ± 2.05 and anemia prevalence was 58.7%. Of the patients, 23.9% took oral nutritional preparations. Anemia was more common in patients receiving oral nutrition preparations and percutaneous endoscopic gastrostomy ($p = 0.001$). When patients were grouped according to their Barthel index, 44.9% were totally dependent. The rate of anemia was higher in the totally dependent group ($p = 0.001$). When assessed in terms of anemia according to the presence of a chronic disease, no statistical difference was detected between the groups ($p = 0.624$).

Conclusion: The prevalence of anemia in the geriatric population receiving home healthcare service was as high as 58.7%. Anemia was detected at a higher rate in totally dependent individuals and in those receiving oral nutrition preparations and percutaneous endoscopic gastrostomy. Anemia is a condition that needs to be evaluated and managed in bedridden and malnourished elderly individuals receiving home healthcare services.

Keywords: Anemia, barthel, home healthcare services, old age

INTRODUCTION

The population is aging fast around the globe and while the population of individuals at the age of 60 years and above was approximately 600 million in 2000, it is projected to double by 2025 and triple by 2050 (1,2). Consequently, health problems commonly seen in the elderly are gaining increasing importance. Home healthcare services refer to the provision of medical examinations, diagnostic testing, treatment, medical care, monitoring, and rehabilitation as well as social and psychosocial counseling in the comfort of patient's home and family environment for individuals who are unable to access healthcare facilities due to chronic diseases

or disabilities. In Türkiye, home healthcare services were formally implemented following a regulation issued in 2005 (3). The aging process is associated with various physiological changes across multiple organs and systems. Hematopoietic system is one of those in which physiological changes are observed as a result of aging. In this system, while hematopoietic cell density in the bone marrow is high during infancy, it significantly decreases with advancing age. Anemia, associated with reduced quality of life, is a common and significant health condition in the elderly. According to the definition of the World Health Organization (WHO, 1968), anemia is a hemoglobin level under 13 g/dL in male individuals and under 12 g/dL in female individuals (4). Anemia

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prevalence in the elderly individuals (hospital, nursing home, community-dwelling, etc.) has been reported as 17% overall, 12% among community-dwelling elderly, 47% among nursing home residents, and 40% at hospital admission (5). The causes of anemia in elderly individuals can be classified into three groups: nutritional anemia (most commonly iron deficiency), anemia of chronic disease (or more precisely, anemia of chronic inflammation), and unexplained anemia. In many cases, anemia arises from multiple contributing factors. If life expectancy is more than one year, a detailed evaluation of anemia is recommended. It is known that anemia in elderly individuals has been related to increased mortality, deterioration of cardiovascular conditions, impaired physical and cognitive function, and high risk of falls and fractures (6). Given these risks, anemia is a factor that should be carefully evaluated and managed, particularly in bedbound elderly individuals receiving home healthcare services.

Our study aims to assess anemia prevalence and association between anemia and both the index for activities of daily living and nutritional status among elderly individuals receiving home healthcare service.

MATERIAL AND METHOD

Study Objective and Design

This study is a retrospective, descriptive and cross-sectional research designed to assess the prevalence of anemia and the association of the index for basic daily living activities for anemia with nutritional status in elderly individuals receiving home healthcare services.

Setting of the Study and Sampling

This study consisted of elderly individuals at the age of 65 years and above who received home healthcare services at the "Home Healthcare Services" unit of Kayseri City Training and Research Hospital between October 2023 and March 2024. Ethical approval for the study was obtained from the Ethics Committee of Kayseri City Hospital (Date and Decision No: 25.06.2024 and 124). Sample size was decided with the G-Power 3.1 software. The minimum required sample size was calculated as 589 participants with $\alpha=0.05$ and $\beta=0.80$, and the study was completed with 593 elderly individuals above the age of 65. Inclusion criteria for the study were elderly individuals aged 65 and older, those who had undergone complete blood count tests, and those who had their index of daily living activities assessed.

Data Collection Tools

Patient Information Form:

A form consisting of demographic data, chronic disease presence and types (if any), nutritional status (normal diet, oral nutritional supplements (ONS), percutaneous endoscopic gastrostomy (PEG)), and Barthel Index scores for Activities of Daily Living (ADL), along with patients'

weight, height and body mass index (BMI) was created by the researchers. Anemia was diagnosed based on the criteria of the WHO: a serum hemoglobin level under 13 g/dL for male patients and 12 g/dL for female patients was considered indicative of anemia (4).

Barthel Index for Basic Activities of Daily Living:

The Barthel Index was developed by Mahoney and Barthel in 1965 and modified by Shah et al. in 1992. The Turkish version was adapted by Küçükdeveci et al. in 2000. This index is a scale used to measure an individual's performance in daily living activities. The index assesses 10 domains for daily living activities: feeding, bathing, self-care, grooming, bowel care, bladder care, transfer from bed to chair and back, use of toilet, stair association, and mobility. Based on the total score, individuals are classified as: 0-20 (totally dependent), 21-61 (severely dependent), 62-90 (moderately dependent), 91-99 (slightly dependent), and 100 (independent). Although it has primarily been developed for neuromuscular and musculoskeletal diseases such as stroke, it can alternatively be used for other conditions (7).

Data Collection

Data of elderly individuals who received home healthcare services were retrospectively collected by two healthcare professional researchers through file scanning method. During home healthcare, routine assessments of the index for daily living activities and regular documentation of nutritional status are recorded in the patients' files.

Data Analysis

SPSS version 22.0 was used for statistical analyses. Whether the distribution of variables was normal or non-normal was assessed with both visual methods (probability plots and histograms) and analytical methods like Kolmogorov-Smirnov tests. Descriptive analyses for normally distributed variables were presented as mean $\pm$ standard deviation (mean $\pm$ SD), while medians and ranges (minimum-maximum) were used to identify non-normally distributed variables. While Independent Sample T-test was used for comparing numerical variables between normally distributed two groups, non-normally distributed numerical variables were identified with Mann-Whitney U test. Chi-square test was employed in comparison of categorical data among the groups. Statistically significant p value was considered <0.05. Pearson's test was used for correlation analyses while analyzing normally distributed numerical variables, and Spearman's Correlation Tests were used while analyzing non-normally distributed variables.

RESULTS

In the study, there were a total of 593 patients aged 65 and above receiving home healthcare services. Of the participants, 60.4% were female. Mean height was 1.62 $\pm$ 0.07 meters, mean body weight was 69.2 $\pm$ 12 kg,

and mean BMI was 26.1±4.6. Mean age was 81.1±8 years. Mean hemoglobin level was 11.8±2.05 g/dL, and anemia prevalence was 58.7%. Among the patients diagnosed with anemia, 56.89% were female (p=0.039). A total of 539 patients had at least one chronic disease. When anemia was assessed in terms of the presence of a chronic disease, no statistically significant difference was found among the groups (p=0.624) (Table 1).

Table 1. Presence of anemia according to gender, age and chronic disease				
		Anemia		p
		Present n (%)	Absent n (%)	
Gender	Male	150 (43.1)	85 (34.7)	0.039
	Female	198 (56.9)	160 (65.3)	
Age		81.6±8.0	80.3±7.8	0.066
Chronic disease	Present	318 (59.0)	221 (41.0)	0.624
	Absent	30 (55.6)	24 (44.4)	
Chi-square test was used; For quantitative data, Student's T-test was used				

When chronic diseases were individually assessed, it was detected that patients with neurological diseases had significantly lower hemoglobin levels (p=0.014) (Table 2).

Table 2. Hemoglobin levels according to chronic diseases				
		n (%)	Mean±std	p
Chronic disease	Yes	539 (90.9)	11.8±2.03	0.264
	No	54 (9.1)	12.1±2.6	
DM	Yes	155 (26.1)	11.82±1.83	0.839
	No	438 (73.9)	11.86±2.13	
HT	Yes	293 (49.4)	11.71±1.96	0.114
	No	300 (50.6)	11.98±2.13	
CAD	Yes	87 (14.7)	12.06±2.14	0.297
	No	506 (85.3)	11.81±2.04	
Neurological diseases	Yes	230 (38.8)	11.68±2.04	0.014
	No	363 (61.2)	12.11±2.04	
Malignancy	Yes	12 (2.0)	10.95±2.02	0.125
	No	581 (98.0)	11.87±2.05	
Asthma/COPD	Yes	89 (15.0)	12.12±2.17	0.178
	No	504 (85.0)	11.80±2.03	
Student's T-test was used; DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease				

While 23.9% of the patients took oral nutrition supplements (ONS), 3.2% had a percutaneous endoscopic gastrostomy (PEG) tube placed. Normal nutrition was more prevalent in the group without anemia whereas ONS and PEG feedings were more commonly used in the anemic group (p=0.001) (Table 3).

Table 3. Prevalence of anemia according to nutritional status			
Nutritional status	Anemia		P
	Present n (%)	Absent n (%)	
Normal nutrition	234 (67.2)	198 (80.8)	0.001
ONS	101 (29.0)	41 (16.7)	
PEG	13 (3.7)	6 (2.4)	
Chi-square test was used; ONS: oral nutrition supplementants, PEG: percutaneous endoscopic gastronomy			

When patients were grouped according to their Barthel Index, 16 patients (2.7%) were classified as totally independent and 266 patients (44.9%) as totally dependent. Anemia prevalence was higher in the totally dependent group (p=0.001) (Table 4).

Table 4. Prevalence of anemia according to barthel index for basic daily living activities

		Anemia		P
		Present n (%)	Absent n (%)	
Barthel Index for basic daily living activities	Totally dependent	164 (47.1)	102 (41.6)	0.001
	Severely dependent	136 (39.1)	83 (33.9)	
	Moderately dependent	39 (11.2)	35 (14.3)	
	Slightly dependent	3 (0.9)	15 (6.1)	
	Totally independent	6 (1.7)	10 (4.1)	
Chi-square test was used				

The correlation between hemoglobin levels and age ($r=-0.125$, $p=0.002$) was weak and negative while the correlation between body weight, BMI, and Barthel Index score was positive ($r=0.131$, $p=0.001$), ($r=0.102$, $p=0.013$), ($r=0.165$, $p<0.001$) (Table 5).

Table 5. Correlation between hemoglobin level and other parameters

		Hg
Age	r	-0.125**
	p	0.002
Height	r	0.058
	p	0.16
Weight	r	0.131**
	p	0.001
BMI	r	0.102*
	p	0.013
Barthel score	r	0.165**
	p	<0.001
* $p<0.05$, ** $p<0.01$; BMI: body mass index, Hg: hemoglobin		

DISCUSSION

A high prevalence of anemia has been stated in similar studies performed on elderly individuals receiving home healthcare services (8,9). High anemia prevalence in elderly individuals is associated with age-related physiological changes, immobility, polypharmacy, malnutrition, and the increasing burden of chronic diseases (10).

In a study by Şimşek Yurt et al. involving elderly individuals receiving home healthcare services, the reported anemia prevalence was 65.4%, while Çevik et al. found a rate of 52.2% in their assessment of nutritional status and laboratory parameters (8,11). These findings align with the anemia prevalence observed in our study. As reported by the WHO, anemia prevalence in individuals aged 65 and above ranges from 10% to 24% and this rate is particularly higher in elderly women. Anemia prevalence in female individuals at the age of 80 and above can rise to as high as 30% (12). The higher anemia prevalence in female gender in our study highlights the impact of gender-related biological and physiological differences on anemia.

The number of chronic diseases and age were identified as key determinants of anemia in a retrospective study assessing anemia prevalence in elderly individuals. Mean age of the participants in our study was 81.1±8

years, and the negative correlation between age and hemoglobin levels indicates the adverse effects of aging on hematopoietic system. In literature, aging has been associated with reduced proliferation of hematopoietic cells, which increases the risk of anemia (13,14). Furthermore, some researchers have indicated that etiology of anemia among the elderly is multifactorial, not limited to chronic diseases alone (10,13). Therefore, the lack of detailed assessments based on the number of chronic diseases in our study may have contributed to the variability of our results. Specifically, chronic conditions such as renal diseases, heart failure, diabetes, cancer, and neurological disorders are associated with high risk of anemia (15). According to our study, individuals with neurological diseases had significantly lower hemoglobin levels, which suggests that anemia in neurological diseases may be related to disease complications and that the low hemoglobin levels could play a role in neurological pathophysiology. The reduction in blood oxygen-carrying capacity due to low hemoglobin levels can lead to cerebral hypoxia, which may trigger neuronal dysfunction and degeneration, thereby increasing exacerbating symptoms (16). Additionally, it has been reported that systemic inflammation resulting from chronic diseases suppresses erythropoiesis, leading to a decrease in hemoglobin levels (17). This mechanism suggests that anemia is not only a consequence but also a factor contributing to the disease process.

Inadequate oral intake, malabsorption and inflammation resulting from chronic diseases may result in both anemia and malnutrition (18). In this context, the need for increased nutritional support in anemic individuals in our study is consistent with these mechanisms. Especially the high rates of anemia in individuals in whom enteral nutrition (ONS and PEG) methods are used suggest that these individuals are at higher risk for nutritional deficiencies.

Oral Nutritional Supplements (ONS) are recommended for individuals who are able to take food orally but get inadequate nutrient intake. Studies have revealed that ONS use reduces malnutrition and improves clinical outcomes (19). Percutaneous Endoscopic Gastrostomy (PEG), on the other hand, is used for long-term enteral nutrition in individuals who are unable to take food orally (20). In our study, anemia prevalence in individuals receiving ONS and PEG was higher, which suggests that both nutritional deficiencies and absorption problems in these

individuals may contribute to anemia. Iron absorption, in particular, may be affected by the functional state of the gastrointestinal system (21).

Moreover, according to the study by Çevik et al., the rates of anemia were higher for patients experiencing malnutrition or those at risk of experiencing malnutrition (11). This result underscores the need to evaluate anemic individuals from not only a hematological perspective but also in terms of metabolic and nutrition-related factors.

It is a known fact that anemia reduces physical performance, decreases quality of life and increases risks such as falls, fractures, and hospitalizations (22,23). Another study of Chaves et al. claimed a significant correlation between low hemoglobin levels and decreased muscle strength, walking speed, and deterioration in daily living activities (24). In our study, the significant relationship between Barthel Index for Basic Daily Living Activities and prevalence of anemia, and the result that anemia prevalence was 47.1% in totally dependent individuals while this rate was decreasing significantly as functional independence increased, may be attributed to these individuals being more vulnerable to both inadequate nutrition and chronic disease burden. The relationship between anemia and dependence is thought to be bidirectional. Anemia may reduce physical capacity, thereby increasing the individual's level of dependency, while inadequate nutrition and immobility in dependent individuals may increase the risk of anemia.

The weak positive correlations found between hemoglobin levels and BMI, body weight, and Barthel Index scores suggest that hemoglobin levels are related to the individual's overall nutritional and functional status. It has also been mentioned in literature that low body weight and malnutrition can increase the risk of anemia (25,26).

While the key strength of this study lies in its contribution to the assessment of anemia prevalence in elderly individuals receiving home healthcare services, the retrospective design of the study, the lack of detailed laboratory data on anemia etiology (such as iron, B12, or folate deficiencies), and the lack of classification of anemia represent some limitations.

CONCLUSION

According to our study, anemia prevalence among elderly individuals receiving home healthcare services is as high as 58.7%. Anemia has been associated with age, presence of chronic diseases, nutritional status, and level of dependence. The significantly lower hemoglobin levels in individuals with neurological diseases highlight the importance of regular monitoring of complete blood counts for this patient group.

The high risk of anemia in patients in whom enteral nutrition methods are used suggests that their nutritional status should be carefully monitored and nutrition strategies should be personalized. The higher prevalence of anemia in bedridden patients indicates that these individuals require a comprehensive evaluation.

Considering the association of anemia with mortality, the progression of cardiovascular diseases, cognitive and physical dysfunction, falls, and fracture risks in elderly individuals, anemia must be evaluated and managed as a significant health issue in those receiving home healthcare services, particularly bedridden individuals. Early diagnosis and appropriate treatment can prevent complications of anemia and enhance quality of life. In this regard, complete blood counts should regularly be conducted, and a multidisciplinary approach to anemia management should be adopted.

Furthermore, more comprehensive and prospective studies should be performed to support our results and explore the effects of anemia on the elderly individuals' quality of life.

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Sex Estimation with Patella Measurements from CT Images

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Abstract

Aim: This study aimed to investigate sex-based differences in an adult Turkish sample by measuring patellar bone size in an adult Turkish sample.

Material and Method: Patella height, width, and depth were measured in cases who underwent knee computed tomography (CT) at Bolu Abant İzzet Baysal University Training and Research Hospital between 2013 and 2023. A total of 102 cases were evaluated. Patellar dimensions, including the heights, widths, and depths of the cases were measured for each case. Statistical analysis was conducted using SPSS version 26.00.

Results: A total of 102 cases including 62 males and 40 females were analyzed in the study. Patella height, width, and modified depth parameters were found to be significantly higher in males ($p < 0.001$). However, since the depth does not affect the accuracy of sex estimation, only the height and width parameters were used for the analysis. For the male sex prediction, 86.7% sensitivity, 71.1% specificity, and 80.6% accuracy rates were obtained with the analysis using height and width parameters. The following discriminant formula was established: "Sex = $1.504 \times \text{Height} + 1.867 \times \text{Width} - 14.218$ ". Separate models were also developed using height and width parameters. When using only height parameters, male sex was predicted with 80% sensitivity, 73.7% specificity, and 77.6% accuracy. The discriminant formula was formulated as follows: "Sex = $2.925 \times \text{Height} - 11.992$ ". When using only the width parameters, the male sex was predicted with 88.7% sensitivity, 75% specificity, and 83.3% accuracy. The discriminant formula was established as: "Sex = $2.987 \times \text{Width} - 12.900$ ". The depth parameters provided 85.5% sensitivity, 52.5% specificity, and 72.5% accuracy with male sex. The formula "Sex = $2.925 \times \text{Height} - 11.992$ " was developed.

Conclusion: Our study demonstrated sex dimorphism in the patellar bone within the Turkish population, with males showing significantly larger patellae than females. An accuracy rate of 80.6% was achieved using all patellar measurements. The findings suggest that the patella may serve as a valuable supplementary tool when used alongside other anthropological methods, enhancing the accuracy and reliability in sex estimation.

Keywords: Forensic medicine, forensic anthropology, identification, sex estimation, patellar bone, computed tomography

INTRODUCTION

Forensic identification has gained importance due to the recent rise in migration and conflicts. Identification is essential for legal and humanitarian reasons. It is a legal requirement to establish the cessation of a person's life. Moreover, enabling the deceased's relatives to conduct a funeral ceremony aligning with their beliefs and traditions facilitates the grieving process with minimal harm. The initial phase in the identification of skeletal remains is establishing the biological profile of the skeleton, which includes determining sex, age, height, and ethnicity. The biological sex estimation process reduces the population to be investigated by half. The biological profile is established and then compared with

information on missing individuals (1,2).

While sex estimation can be achieved at a rate of 98-100% in cases where the entire skeleton or both the pelvis and skull are preserved, the remains examined in a forensic context may have compromised integrity (1-5). Compact and durable bones become essential for anthropological studies in fragmented, burned, or otherwise damaged cases. The patella has a potential for anthropological analysis thanks to its compact and distinctive structure and location between two solid long bones, such as the femur and tibia (6-9).

Population specificity in forensic anthropology underscores the variation in skeletal morphology across

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different ethnic and regional groups. Sexual dimorphism, while present universally, manifests differently depending on genetic and environmental factors, leading to variations in bone structure and size. Therefore, it can be argued that population-specific standards have become necessary to determine sex from skeletons. However, it is recommended that standards specific to one population should not be used in another population. Therefore, the need for prior information regarding the population group of the skeleton to be examined can be seen as a drawback in using population-specific standards in a forensic context (10-14). This study aims to determine the differences between sexes by measuring the patellar height, width, and depth.

MATERIAL AND METHOD

This study was conducted at Bolu Abant İzzet Baysal University İzzet Baysal Training and Research Hospital (BAIBUTRH). Ethics approval dated 22.09.2023 and numbered 409 was obtained from Bolu Abant İzzet Baysal University Clinical Research Ethics Committee for the study. The study was designed in accordance with the Declaration of Helsinki. Patella height (vertical length of the patella measured between its most superior and most inferior anatomical points), width (transverse width of the patella measured between its most medial and most lateral anatomical points), and depth (anteroposterior thickness of the patella measured from the most anterior to the most posterior anatomical point) were measured in cases who underwent knee computed tomography (CT) at BAIBUTRH between 2013 and 2023. Using G*Power version 3.1.9.6, the required sample size was calculated based on an effect size of 0.15, a power of 0.90, an alpha level of 0.05, and three independent variables, yielding a minimum of 99 participants. A total of 102 individuals were included in the study. All CT images were obtained using a 64-slice scanner (Revolution Evo, GE Healthcare, Milwaukee, Wisconsin, United States) with patients in the supine position, including the entire patella and fibular head in the scan range. Scans were acquired using a high-resolution bone algorithm with a slice thickness of 1.25 mm, a reconstruction interval of 0.625 mm, at 120 kV, and with tube current modulation. Images were post-processed

using multiplanar reconstruction and three-dimensional volume rendering (3D VR) techniques on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare, Milwaukee, WI, USA). Observers were allowed to enlarge the CT slices and adjust image contrast and screen brightness during measurements to optimize visualization. A total of 102 cases were accessed. Height measurements could not be made in four cases due to missing sections. The widths and depths of these cases were measured, and analyses were made accordingly. The suitability of the parameters for normal distribution was checked with the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test was used for comparisons according to sex. In the display of parameters, mean, standard deviation, and minimum-maximum values or median and interquartile range were used depending on the distribution. A linear discriminant analysis model was established. SPSS 26.00 program was used in the statistics, and p<0.05 was determined as the significance level.

RESULTS

102 cases, 62 males and 40 females were included in the study. The height parameter could not be measured in four cases due to limited access to CT image sections. Fifteen days after the initial measurement, the same operator remeasured 25% of the randomly selected subjects. The Inter/Intra-Class Correlation Coefficient (ICC) was used to assess inter-observer and intra-observer reliability, aiming to minimize result bias. The ICC in this study ranged from 0.987 to 0.996, indicating excellent reliability according to the interobserver reliability classification proposed by Koo and Li (15). Bonferroni transformation ($\alpha=1/x$) was applied to the depth parameter that did not show a normal distribution (Statistics: 0.974; p=0.042). It was observed that the modified depth parameter followed a normal distribution (Statistics: 0.987; p=0.421).

Comparisons by sex were made with the Student's t-test. Patella height, width, and modified depth parameters were found to be higher in men (p<0.001). Descriptive statistics and analysis results of the measurements are shown in Table 1.

Table 1. Sex wise descriptive statistics of patellar dimensions										
	Male				Female				t	p
	Mean	Std	Min	Max	Mean	Std	Min	Max		
Height	4.32	0.36	3.65	5.11	3.74	0.30	3.13	4.40	8.191	<0.001
Width	4.55	0.35	3.69	5.43	3.94	0.32	3.28	4.54	8.737	<0.001
Modified depth	0.46	0.04	0.37	0.57	0.51	0.04	0.41	0.60	-4.888	<0.001

Linear discriminant analysis was run with height, width, and modified depth parameters. When canonical discriminant functions were examined, it was seen that the eigenvalue was 0.985, the canonical correlation was 0.704, Wilks' lambda was 0.504, the chi-square was 64.792 and the p-value was <0.001. It was determined that patellar depth did not affect sex estimation (standardized canonical discriminant function coefficient: -0.007). The analysis was conducted with width and height parameters. The

correlation coefficient was measured as 0.520. The male centroid was found to be 0.782, the female centroid was -1.234, and the cut-off value was determined to be -0.226. For the male sex, 86.7% sensitivity, 71.1% specificity, and 80.6% accuracy rates were obtained. Classification statistics are shown in Table 2. The discriminant formula was established as follows:

Sex=1.504xHeight + 1.867xWidth-14.218

Table 2. Classification table from linear discriminant function analysis for height and width				
		Predicted group membership		
		Male	Female	Total
Original	Male	86.7% (52)	13.3% (8)	60
	Female	28.9% (11)	71.1% (27)	38
Cross-validated	Male	85% (51)	15% (9)	60
	Female	28.9% (11)	71.1% (27)	38

Separate models were run for the height and width parameters (0.514 and 0.631, respectively), for which the standardized canonical discriminant function coefficients are substantially high. When the canonical discriminant functions of the model built with the height value were examined, it was seen that the eigenvalue was 0.699, the canonical correlation value was 0.641, Wilks’ lambda was 0.589, the chi-square value was 50.612, and the p-value was <0.001. The male centroid was found to be 0.658, the female centroid was -1.040, and the cut-off value was determined to be -0.191. Male sex was detected with 80% sensitivity, 73.7% specificity, and 77.6% accuracy. Classification statistics are shown in Table 3. The discriminant formula was derived as follows:

$$\text{Sex}=2.925 \times \text{Height}-11.992$$

Table 3. Classification table from linear discriminant function analysis for height				
		Predicted group membership		
		Male	Female	Total
Original	Male	80% (48)	20% (12)	60
	Female	26.3% (10)	73.7% (28)	38
Cross-validated	Male	80% (48)	20% (12)	60
	Female	26.3% (10)	73.7% (28)	38

When the canonical discriminant functions of the model built with the width value were examined, it was seen that the eigenvalue was 0.813, the canonical correlation was 0.670, Wilks’ lambda was 0.551, chi-square was 59.227, and the p-value was <0.001. The male centroid was determined as 0.717, the female centroid as -1.112, and the cut-off value was set at -0.197. The male sex was detected with 88.7% sensitivity, 75% specificity, and 83.3% accuracy. Classification statistics are shown in Table 4. The discriminant formula was established as follows:

$$\text{Sex}=2.987 \times \text{Width}-12.900$$

Table 4. Classification table from linear discriminant function analysis for width				
		Predicted group membership		
		Male	Female	Total
Original	Male	88.7% (55)	11.3% (7)	62
	Female	25% (10)	75% (30)	40
Cross-validated	Male	88.7% (55)	11.3% (7)	62
	Female	25% (10)	75% (30)	40

When the canonical discriminant functions of the model built with the depth value were examined, it was seen that the eigenvalue was 0.268, the canonical correlation was 0.460, Wilks’ lambda was 0.798, chi-square was 23.634, and the p-value was <0.001. The male centroid was determined as 0.412, the female centroid as -0.638, and the cut-off value was set at -0.113. The male sex was detected with 85.5% sensitivity, 52.5% specificity, and 72.5% accuracy. Classification statistics are shown in Table 5. The discriminant formula was established as follows:

$$\text{Sex}=23.644 \times 1/\text{Depth}-11.310$$

Table 5. Classification table from linear discriminant function analysis for depth				
		Predicted group membership		
		Male	Female	Total
Original	Male	85.5% (53)	14.5% (9)	62
	Female	47.5% (19)	52.5% (21)	40
Cross-validated	Male	85.5% (53)	14.5% (9)	62
	Female	47.5% (19)	52.5% (21)	40

DISCUSSION

In Akhlaghi et al.’s study in Iran, involving 113 cases, it was observed that patella height and width were higher in all cases, while patella depth was found to be higher in men in the 20-39 age group and the ≥65 age group (16). The study of Moneim et al. showed that the patella’s height and width were greater in men than in women (17). In the study by Zhan et al. with 300 cases in China, patella height, depth, width, and volume were all larger in men (9). In a study of 161 cases conducted by Rahmani et al. in Iran, patellar height, depth, and width were found to be more significant in men (6). In the study by Peckmann and Fisher, which measured the patella height, width, depth, joint surface width, and height of 200 skeletons, a significant difference was found between the sexes in favor of men in all measurements (8). The study by Michiue et al. in Japan with 220 CT images showed that height, depth, and volume values were larger in men (18). All papers included in the meta-analysis by Fernandez et al. revealed a significant difference between sexes in all patella measurements (19). In a study with a Portuguese sample, males showed larger dimensions in patella sizes (14). In Kemkes-Grottenthaler’s study, it was observed that male patellas were larger (13). Teke et al. showed that all measurements of males were greater than females (20). The study by Öner et al. reported that all anteroposterior, craniocaudal, transverse length and volume values were greater in men (21). In our study, we measured all patella sizes to be larger in men, consistent with existing literature.

Although there is a recognized difference between sexes in patella height and width, the distinction is less pronounced for depth. Akhlaghi et al. observed that the accuracy rate for patellar depth measurements (74.3%) was lower compared to width (91.2%) and height (89.4%) (16). Zhan et al. also reported that patella and width accuracy rates

(85.7% and 82.3%, respectively) were higher than patella depth (73.1%) (9). Rahmani et al. correctly classified the sexes 84.5% with patellar width, 75.2% with patellar height, and 65.5% with patellar depth (6). In our study, consistent with the literature, more accurate rates were achieved with width (83.3%) and height (77.6%) measurements than with depth (72.5%). In our study, it was determined that patella depth had almost no effect on sex determination. This could be attributed to the nominal values of patellar height and width being greater than that of depth, potentially resulting in a lower difference between sexes in depth measurements.

In a study conducted on the Iranian population, sex was determined with a rate of 92.9% accuracy using discriminant analysis based on patella measurements (16). A study on the Chinese population demonstrated that accurate estimation, up to 85.7%, could be achieved with patellar volume (9). In Rahmani et al.'s study using MR images, discriminant analysis based on patella width and height classified males correctly at 81.0%, females at 90.2%, and the entire population at a rate of 85.7% (6). In Peckmann and Fisher's study, sex was estimated 85% accurately by discriminant analysis using all variables (8). In another study conducted on the Spanish population, it was shown that the accuracy rate of sex estimation from the patella was up to 82% (22). In a study on the Japanese population, the highest accuracy was achieved with the left patella volume at 87.7%, followed by the right patella volume at 85.5%, the left patella height at 82.3%, and the right patella height at 80.9% (18). Introna et al.'s study on dry bones reported an 83.8% accurate sex determination rate with the analysis performed with maximum width and thickness, while other analyses contained a higher margin of error (12). In Kemkes-Grottenthaler's work, the patella yielded an initial sexing accuracy of 84%, which, when adjusted for methodological considerations like sample size using statistical techniques, the accuracy decreased to only 74–78% (13). Indra et al. were able to achieve an accuracy rate of 83.8% (10). Maio et al. showed that, the maximum height stands out with 77.0% correct sex estimation, reaching 98.0% when applied to the new sample. The linear discriminant function analysis showed 80.2% accuracy after cross-validation and 96.0% when applied to the independent sample (14). The study by Teke et al. determined males with 87% accuracy and females with 91% accuracy. They also achieved prediction accuracy of 86% and 83% for height, 77% and 81% for depth, and 89% and 84% for width in women and men, respectively (20). In the study by Oner et al. using the decision tree algorithm, males were predicted with a rate of 98.2% and females with 98.4% (21). In our study, the rate of 80.6% was attained with the patellar height and width model.

Limitations of the Study

The results in this study, below the 85% accuracy rate achieved in some previous studies, may be attributed to the relatively low number of cases (n=98) and the

disparity in the number of female (n=38) and male (n=60) cases. Additionally, the single-center conduct of the study imposes limitations in terms of population diversity.

CONCLUSION

Our study demonstrated sex dimorphism in the patellar bone within the Turkish population, with males showing significantly larger patella than females. In our study, biological sex estimation achieved an accuracy rate of 80.6% using all patella measurements. However, the associated error rate of 19.4% is notably high for forensic anthropological applications and falls below the acceptable threshold for forensic medicine practices. Therefore, the findings indicate that, within the Turkish population, relying solely on the patella for sex determination in forensic contexts is not advisable. However, the patella may serve as a valuable supplementary tool alongside other anthropological methods, enhancing the accuracy and reliability of biological sex estimation. It is essential to recognize that osteometric data are population-specific, and the 80.6% accuracy rate observed in this study requires validation in diverse populations.

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Retrospective Review of Lumbar Disc Surgeries Performed Under Spinal Anesthesia During the COVID-19 Pandemic: Can Spinal Anesthesia Be a Practical Alternative for Surgical Procedures in Pandemic Periods?

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Abstract

Aim: Recent studies report that spinal anesthesia may be an alternative to general anesthesia in lumbar surgeries. Considering the benefits that spinal anesthesia provides to patients over general anesthesia, it is a positive development. Depending on the importance and priority of the work to be done, surgical interventions must be performed when necessary. In the present study, a retrospective review was made regarding Lumbar Disc Herniation (LDH) surgeries under spinal anesthesia in our hospital during the COVID-19 pandemic.

Material and Method: LDH surgeries performed under spinal anesthesia in 184 patients between March 14, 2020, and December 31, 2022, were evaluated retrospectively in the present study.

Results: A total of 196 patient files were scanned and the files of 184 were examined retrospectively. A total of 12 patients were excluded from the study because of insufficient data. It was found that the surgery times of patients with surgical levels L5-S1 were significantly higher. The first postoperative analgesia requirement was significantly later in patients who underwent surgery at the L5-S1 level. Ephedrine was administered to 13 of the patients and atropine was administered to 14 of them. Perioperatively, 14 of the patients required additional analgesia. Postspinal headache developed in 16 of the patients and urinary retention developed in 12. SAP, DAP, and MAP of the patients decreased significantly after the intraoperative spinal anesthesia.

Conclusion: The results of the present study showed that spinal anesthesia is safe in awake lumbar disc surgery patients, which supports the increasing literature data emphasizing the superiority of spinal anesthesia in awake lumbar surgery procedures. It was also shown that spinal anesthesia can be preferred for sustainable surgery during pandemic periods when the need for ventilators is intense and opportunities are limited.

Keywords: Spinal anesthesia, lumbar disc hernia, COVID-19, pandemic period, sustainable resource use

INTRODUCTION

Many anatomical changes occurred after bipedalism in the process of human evolution. The tempo of human evolution has caused some of these changes to remain uneliminated through natural selection. Low back pain is just one of the undesirable consequences of these changes. Low back pain is a common problem in society and causes loss of workforce. Its lifetime prevalence reaches 80% and annual hospital admission rates in the adult population reach 15% (1-3). One of the most common causes of low back pain is Lumbar Disc Herniation (LDH), which occurs as a result

of the herniation of the intervertebral disc into the spinal canal. If LDH causes severe motor losses and severe sciatica that does not resolve within 3-4 weeks, surgical intervention is recommended (4).

Lumbar disc surgery is among the most common spine procedures and is usually performed under general anesthesia (5). Some surgeons and/or patients prefer general anesthesia for their comfort, but recently, they prefer spinal anesthesia in compatible and selected patients who do not need general anesthesia (e.g., in unilateral/single-level discectomies with short surgery times) (6).

CITATION

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We have observed that the risk of pulmonary complications has increased significantly due to COVID-19 during the pandemic period, and this has created anxiety for patients and surgeons. The increased preference for spinal anesthesia in LDH surgeries performed in our hospital during the pandemic period supports our observation.

The present study aimed to retrospectively examine LDH surgeries performed under spinal anesthesia during the COVID-19 pandemic.

MATERIAL AND METHOD

The material of the study consists of the retrospective evaluation of the records of the patients who underwent LDH surgeries performed under spinal anesthesia between March 14, 2020, and December 31, 2022. After obtaining ethics committee approval from Karabük University, Non-Interventional Ethics Committee (No: 2023/1271, Date: 24.02.2023) at Karabük Training and Research Hospital, a retrospective study was designed in light of data obtained from the surgery room and archives of Karabük University, Training and Research Hospital. Spinal anesthesia of the patients was performed electively by an experienced specialist or an anesthesia assistant who had completed at least 2 years of experience under the surveillance of a specialist. American Society of Anesthesiologists (ASA) I-III patients over the age of 18, who underwent LDH surgery under spinal anesthesia within the specified dates, were included in the study. The data obtained from patient files such as ASA scores IV and above, patients with a history of allergies, patients with respiratory or heart failure, or patients who underwent general anesthesia because of long surgery times were not evaluated. Age, sex, ASA scores, preoperative, intraoperative, and post-operative hemodynamic data of the cases (systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP), heart rate peaks, saturations), intraoperative additional sedation needs, whether inotropes were needed after spinal anesthesia, at what time and how often post-operative analgesia was needed, and discharge times were recorded.

The patients were tested for COVID-19 with the Polymerase Chain Reaction (PCR) Test. Before spinal anesthesia was applied to all patients, 6-8 kg ml⁻¹ crystalloid fluids were administered i.v. in the preoperative waiting room. All patients were administered an antiemetic protocol with pantoprazole and ondansetron.

Anesthesia Technique

After the patients were taken to the surgery room, it was found in the file reviews that pulse oximetry, non-invasive blood pressure monitoring, and electrocardiogram were applied as standard monitoring on the stretcher before being taken to the surgery table. It was also understood that the patients were placed in a sitting position and the area to be treated was sterilized and covered in line with the rules of asepsis and 12.5-15 mg hyperbaric bupivacaine was administered with a 15 G Quincke spinal needle from the 3rd or 4th lumbar vertebra, depending

on the level of the surgery. The patients were kept in the supine position for approximately 10 minutes and were then taken to the surgery table in the prone position after the block level reached the T10 level. Also, 0.02-0.04 mg kg⁻¹ i.v. midazolam was administered in the presence of anxiety, and 1-2 mcg kg⁻¹ fentanyl i.v. was administered in the presence of pain.

All patients were taken to the postoperative recovery room after the surgery was completed and were then transferred to the wards after the block levels reached the L5. All patients were discharged after being monitored for at least 24 hours in the ward.

Statistical Analysis

In the statistical analysis of the data, descriptive statistics were determined. The data were defined by determining the mean and standard deviation in demographic data, and percentage amounts in non-parametric data. The Kolmogorov-Smirnov Test was applied to determine the compliance of the data with normal distribution. In the case of comparison of three or more variables, ANOVA was performed for parametric data, while Kruskal Wallis test was applied for non-parametric data, if it did not meet the normality assumption depending on the nature of the data, or Chi-square test was applied according to the structure of the data. The critical value for significance was determined as 0.05 and all analyses were made in the SPSS 23V statistical program.

RESULTS

The data of 184 patients who underwent LDH surgery were examined retrospectively in the study. Demographic data, ASA scores, presence of comorbidities, and drug use status of the patients are given in Table 1. A total of 49.5% of the patients included in the study were female and 50.5% were male. The average age of the patients was 48.7±8.3. 66.3% of the patients had ASA II scores, 50.5% of the patients faced comorbidity, and 44.6% used at least one medication.

Surgery times according to spinal and surgical levels are given in Table 2. When the table is examined, spinal anesthesia was performed in 91.8% of the patients at the L3-4 level and in 8.2% at the L4-5 level. Surgery was performed at the L4-5 level in 55.9% of the patients, at the L5-S1 level in 40.2%, and the L3-4 level in 3.9%. The average surgery time of the patients was 90 minutes and was significantly higher in patients who underwent surgery at the L5-S1 level.

The spinal anesthesia levels, surgical procedure levels, and first postoperative analgesia administration times are given in Table 3. When the table is examined, it is seen that 57.4% of the patients who underwent spinal anesthesia at the L3-4 level underwent surgery at the L4-5 level, 38.5% at the L5-S1 level, and 4.1% at the L3-4 level. The differences between all surgical levels at the L3-4 spinal level were found to be statistically insignificant. Among the patients who underwent spinal

anesthesia at the L4-5 level, 60% underwent surgery at the L5-S1 level, and 40% underwent surgery at the L4-5 level. The first postoperative analgesia requirement was significantly later in patients who underwent surgery at the L5-S1 level.

In some cases, patients might have intraoperative complications and need for sedoanalgesia. Knowing these is important in terms of directing and managing the transactions to be performed. Intraoperative complications and sedoanalgesia needs of the patients are given in Table 4. Ephedrine was administered to 13 of the patients and atropine was administered to 14 of them. Perioperatively, 14 patients required additional analgesia. The relationship between the patients' need for additional intraoperative analgesia, spinal level, and surgical level is given in Table 4.

Postoperative complications such as headaches and urinary retention might occur during surgeries. Eliminating these with immediate intervention is important for patient health. Postoperative complications of the evaluated patients are given in Table 5. Postspinal headache developed in 16 of the patients and urinary retention developed in 12. The differences observed between postoperative complications were found to be statistically significant.

The hemodynamic data of the patients and the graphical views of the data are given in Table 6. SAP, DAP, and MAP of the patients decreased significantly after intraoperative spinal anesthesia. Average pulse rates also decreased but were not statistically significant. No changes were detected in the peripheral saturated oxygen levels of the patients.

Table 1. The demographic data, ASA scores, presence of comorbidities, and drug use status of the patients			
Characteristics		Values	Significance (P)
Age (years) (Mean±SD)	Mean	48.7±8.3	P>0.05 (Insignificant)
	Female	48.6±10.2	
	Male	49.0±6.9	
Sex (n/%)	Female	91 (49.5)	P>0.05 (Insignificant)
	Male	93 (50.5)	
ASA (Score/%)	I	49 (26.6)	P<0.05 (Significant)
	II	122 (66.3)	
	III	13 (7.1)	
Weights of the patients (kg)	Mean weight	76.7	P>0.05 (Insignificant)
	Female	81.8	
	Male	71.8	
Comorbidities (n/%)	Yes	93 (50.5)	P>0.05 (Insignificant)
	No	91 (49.5)	
Medication status (n/%)	Yes	82 (44.6)	P>0.05 (Insignificant)
	No	102 (55.4)	

Table 2. Surgery times according to spinal and surgical levels						
Spinal level	n/%	Surgical Level	n/%	Significance (P)	Surgery time (minute)	Significance (P)
L3-4	169 (91.8)	L3-4	7 (4.1)	P<0.05 (Significant)	84.28	P>0.05 (Insignificant)
		L4-5	97 (57.4)		85.87	
		L5-S1	65 (38.5)		89.45	
L4-5	15 (8.2)	L4-5	6 (40.0)	P>0.05 (Insignificant)	73.31	P<0.05 (Significant)
		L5-S1	9 (60.0)		90.00	

Table 3. The spinal anesthesia, surgical procedure levels, and first postoperative analgesia application times of the patients			
Spinal level	Surgical level	Time to first analgesia need (minute)	Significance (P)
L3-4	L3-4	461.43	P>0.05 (Insignificant)
	L4-5	444.85	
	L5-S1	464.88	
L4-5	L4-5	406.67	P<0.05 (Significant)
	L5-S1	515.55	

Table 4. The intraoperative complications and sedoanalgesia needs of the patients

Spinal level	Surgical level	Number of patients administered ephedrine (%)	Significance (Chi-square)	Number of patients administered atropine (%)	Significance (Chi-square)	Intraoperative additional analgesia			Significance (Chi-square)
						Total	Yes	No	
L3-4	L3-4	1 (0.59)	P>0.05 (Insignificant)	1 (0.59)	Insignificant	7	0	7	P<0.05 (Significant)
	L4-5	8 (4.73)		7 (4.40)		97	7	90	
	L5-S1	2 (1.18)		5 (2.95)		65	4	61	
L4-5	L4-5	1 (6.67)	P>0.05 (Insignificant)	0 (0.00)	Insignificant	6	2	4	P>0.05 (Insignificant)
	L5-S1	1 (6.67)		1 (6.67)		9	1	8	

Table 5. Some postoperative complications of the patients

Postoperative complications	Total	Headache		Urinary retention	
		Yes	No	Yes	No
	184	16	168	12	172
Significance (Chi-Square)		P<0.05 (Significant)		P<0.05 (Significant)	

Table 6. The hemodynamic data and graphical views of the patients

Characteristics	Measurement times	Measured mean values (minute)	Significance (P)
Systolic arterial pressure (SAP) mmHg	Preoperative period	142.36	P<0.05 (Significant)
	5 min	129.73	
	15 min	119.94	
	30 min	119.49	
	Postoperative period	124.76	
Diastolic arterial pressure (DAP) mmHg	Preoperative period	84.59	P<0.05 (Significant)
	5 min	76.03	
	15 min	70.00	
	30 min	69.11	
	Postoperative period	73.25	
Mean arterial pressure (MAP) mmHg	Preoperative period	104.04	P<0.05 (Significant)
	5 min	93.78	
	15 min	86.89	
	30 min	86.01	
	Postoperative period	90.36	
Pulse rates	Preoperative period	84.51	P>0.05 (Insignificant)
	5 min	84.59	
	15 min	82.14	
	30 min	81.27	
	Postoperative period	80.49	
Peripheral saturated oxygen levels	Preoperative period	97.61	P>0.05 (Insignificant)
	5 min	98.03	
	15 min	97.58	
	30 min	98.10	
	Postoperative period	98.15	

DISCUSSION

When the data of 184 patients to whom we applied spinal anesthesia because of LDH surgery were examined, it was determined that spinal anesthesia was sufficient for

all of the patients. None of the patients required general anesthesia. This result was found to be important because it showed that spinal anesthesia was successful. The present study shows that spinal anesthesia provides

adequate anesthesia in LDH surgeries, increases patient safety, and clinical results are at least as good as those of patients undergoing general anesthesia. It was considered very important that these results were compatible with the studies in the literature (7-11).

In our present day, general anesthesia is still the most commonly used method in spinal surgeries. This may be because of reasons such as spinal surgeries taking a long time, the possibility of bleeding being high, surgical procedures requiring good airway control, and patient movements during surgery (12,13). However, in recent years, the development of new surgical methods and increased familiarity with the spinal region have increased the popularity of spinal anesthesia practices, as surgical procedures are shorter and are performed in a more controlled manner (14).

The incidence of hypotension is more common during spinal anesthesia than during general anesthesia. However, this complication can be eliminated by appropriate fluid replacement, not keeping the surgical procedure long, and appropriate patient positioning (15). The patients also developed hypotension that did not require significant intraoperative inotropic support, which was evaluated as spinal anesthesia minimally affecting hemodynamics in selected patients. There are publications in the literature stating that this type of hypotension, which does not impair hemodynamics, increases surgical vision (16). Only 14 of the cases developed bradycardia requiring atropine administration. 13 of the patients developed hypotension requiring ephedrine administration. It was thought that these complications were not related to the surgical procedure performed but were events that could be observed during spinal anesthesia.

A total of 14 patients required additional intraoperative analgesia in the study. However, it is noteworthy that at surgical levels where the surgery time is short, the need for additional analgesia is less, which was interpreted as the effect of surgery duration on the need for additional analgesia. In addition, the relationship between the level of spinal anesthesia and the requirement for intraoperative additional analgesia was analyzed, and it was observed that lower spinal levels were associated with increased analgesia needs, especially in longer surgeries. This may suggest that both the anatomical level of anesthesia and surgical duration play a role in intraoperative analgesia demand.

It is already known that complications such as respiratory problems, nausea and vomiting, deep vein thrombosis, and bleeding are less common in spinal anesthesia than in general anesthesia (17). Opioids and inhalation agents increase nausea and vomiting. None of the patients had nausea and vomiting that would prolong hospitalization, nor did any of the patients have bleeding that required blood product transfusion in the present study.

Headache and urinary retention after spinal anesthesia are serious complications and are annoying for

anesthesiologists and will prolong the hospital stays. In the present study, 2 patients had severe headaches that prolonged their hospital stays. However, these patients responded well to medical treatment. Urinary retention occurred in 12 of the patients. These patients were treated with a urinary catheter. There was no urinary retention that prolonged hospital stays. The rates of urinary retention and headache in the present study are consistent with the literature data (18-20). The incidence of postspinal complications observed in our study—specifically postdural puncture headache (PDPH) in 8.7% of patients and urinary retention in 6.5%—is generally consistent with previously published data. In the literature, the incidence of PDPH has been reported to range between 0.8% and 5%, depending on factors such as needle type, patient age, and duration of surgery (21). Similarly, studies have reported urinary retention rates of approximately 2–7% following spinal anesthesia, particularly in urologic and orthopedic cases (22). The average surgical duration of 90 minutes in our study likely contributed to these outcomes being within the expected clinical range. These findings support the safety and predictability of spinal anesthesia in lumbar disc surgeries under standard conditions.

There are some difficulties with spinal anesthesia in LDH surgeries. Postoperative neurological examination and the pressure and stress it causes on anesthesiologists are very important. This may push anesthesiologists away from spinal anesthesia (23). However, several advantages of spinal anesthesia compared with general anesthesia have been reported. Some studies reported it to be superior in relieving postoperative pain, maintaining hemodynamic stability, and reducing postoperative adverse effects (24). Some other advantages include superior glycemic control, preservation of intraocular pressure, and cost reduction in diabetic patients. It also decreases the possibility of pressure injuries that may occur because of a prone position (13,25).

Many surgical procedures decreased because of the COVID-19 pandemic along with spinal surgeries. Most elective cases were postponed. There were significant disruptions in pharmaceutical and material manufacturers and suppliers, and most of the available resources were transferred to the fight against COVID-19. For these reasons, there were efforts to establish guidelines for appropriate courses of action when considering specific surgical spine pathologies. Validation of such guidelines and retrospective analyses are critical to establishing evidence-based systems for spine care in the event of a future viral outbreak (26,27).

During the COVID-19 pandemic, where ventilator and intensive care unit (ICU) capacities became critically limited, none of the patients in our study who received spinal anesthesia required postoperative ventilator support or ICU admission. This highlights the potential of spinal anesthesia to preserve essential hospital resources in times of medical crisis. Moreover, surgical procedures

under general anesthesia often involve aerosol-generating procedures (AGPs) such as endotracheal intubation and extubation, which significantly increase the risk of viral transmission to healthcare personnel. In contrast, spinal anesthesia eliminates the need for airway manipulation and thereby reduces this transmission risk. Studies in the literature have reported spinal anesthesia as a safer alternative for both COVID-19 positive and negative patients during the pandemic. For instance, it has been demonstrated that spinal anesthesia can be safely used with minimal aerosol exposure and without compromising surgical outcomes (28,29). Therefore, spinal anesthesia should be considered not only as a clinically effective anesthetic method but also as a strategic option in resource-limited and high-risk pandemic settings.

There are data that spinal surgeries with spinal anesthesia decrease costs, decrease the length of hospital stay, and decrease the use of healthcare resources (30). For this reason, in the setting of any potential future medical limitations, awake spinal surgery is likely to increase a hospital's capacity to perform spinal surgical procedures (31). In this sense, spinal anesthesia has the potential to play an important role in spinal surgery procedures in the event of a future pandemic (32).

The present study had some limitations. Firstly, the study had a retrospective design. Although only LDH surgeries were included in the study, they were performed by different surgeons. The anesthesia procedure was also performed by more than one anesthesiologist. The intraoperative sedation preferences of anesthesiologists may differ. Also, the data on complications were obtained by retrospectively examining inpatient, surgery room notes, and outpatient notes rather than a single database. Patient satisfaction and surgical satisfaction could not be examined.

CONCLUSION

In conclusion, it is considered to be an alternative to general anesthesia in LDH surgeries, provided that appropriate communication is established between the surgical team and the patient. Also, the present study shows that spinal anesthesia may play critical roles in lumbar surgeries in future epidemics.

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Conflict of interest: The authors have no conflicts of interest to declare.

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Determination of the Effect of ShotBlocker in Reducing Intramuscular Injection Pain in Adult Patients: A Randomized Controlled Trial

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Abstract

Aim: This study aimed to evaluate the effect of the ShotBlocker device on pain intensity due to intramuscular injection in adult patients presenting to the emergency department.

Material and Method: The study was conducted as a randomized controlled trial. Data were collected from patients who presented to the emergency department of a public hospital in southern Türkiye and volunteered to participate in the study. Participants were randomly assigned to intervention and control groups using a randomization program. Data collection tools included a Personal and Medication Information Form and the Visual Analog Scale.

Results: 80 participants were equally distributed in the intervention and control groups. Gender distribution was equal across both groups. The mean age of participants was 42.20 ± 14.60 years in the intervention group and 47.00 ± 15.10 years in the control group. Diclofenac sodium was the most frequently administered medication in both groups (Intervention: 24, Control: 22). It was determined that the mean pain scores of the participants in the intervention group were significantly lower than those in the control group. Additionally, within the intervention group, pre- and post-injection pain scores varied according to gender, marital status, educational level, income status, and medication type.

Conclusion: The ShotBlocker appears to be a potentially effective non-pharmacological method for managing pain associated with intramuscular injections in adult patients. Its implementation in emergency care settings may contribute to improving patient comfort and enhancing pain management strategies. This study's findings are limited by its single-center design, focus solely on post-injection pain, exclusion of other outcome variables, and reliance on self-reported pain assessment.

Keywords: ShotBlocker, emergency department, pain, intramuscular injection, nursing

INTRODUCTION

One of the most commonly used treatment methods in injection applications is Intramuscular Injection (IMI) (1). IMI accelerates the treatment process and facilitates drug absorption by enabling systemic drugs to be administered into muscle tissue (2). Although IMI is considered a simple technique, the most common effect observed at the injection site after administration is pain (3). There are two reasons for the pain that occurs during IMI. The first is the penetration of the needle into the muscle tissue, and the second is the administration of the drug into the tissue (4). This pain can cause anxiety in patients or reduce their acceptance of the treatment. It is therefore important to reduce this pain caused by the application.

Nurses are health professionals who play a primary role in helping adults cope with negative experiences during needle-related procedures (5). Pain relief is one of the fundamental elements of nursing care, and in this context, nurses need to master effective pain control strategies (6). Nurses can take an active role in controlling pain caused by IMI using non-drug methods within the framework of their professional responsibilities. These methods are quite diverse. For this purpose, different applications such as local ice application (7), manual pressure application (8), acupuncture (9), skin-to-skin care (kangaroo care) (10) and lidocaine/prilocaine-containing creams (11) are seen in the literature. These methods are advantageous in terms of being low cost, easy to apply and having a low risk of side effects (12).

CITATION

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In recent years, ShotBlocker has also gained interest in reducing IMI pain. ShotBlocker is a flexible, low-tech, cost-effective, drug-free plastic device with skin contact points and a central hole for injection (13). Since the contact points in this device are blunt, it does not damage the skin and acts according to the gate control theory. According to the gate control theory; the physical contact stimulus before the injection reaches the spinal cord before the injection pain and closes the gates against pain transmission (14). Therefore, this theory suggests that pain is not only a physiological process, but that "gating" mechanisms in the nervous system affect pain perception by regulating sensory signals. Therefore, it becomes possible to relieve pain by applying ShotBlocker before the injection. Therefore, it is possible to relieve pain by applying ShotBlocker before injection. Therefore, it is assumed that the use of ShotBlocker to reduce pain during injection is related to the gate control theory of pain. Studies have reported that no side effects were observed as a result of the use of ShotBlocker and that it was effective in patients (15-17). However, it is seen that more studies are needed in terms of its effectiveness or side effects. Since there are limited studies on the use of ShotBlocker, especially in the adult group, it is recommended that the subject be scientifically investigated more deeply in terms of the adult patient group and that non-pharmacological methods be used to increase patient comfort and improve the quality of health services in IMI frequently applied by nurses during the treatment process. In this context, it is important to investigate the effects of interventions such as ShotBlocker application before injection on pain.

This study aims to investigate the effect of ShotBlocker on injection pain during intramuscular administration of diclofenac sodium and metamizole sodium, which are frequently used in emergency department settings.

MATERIAL AND METHOD

Study Design and Protocol

This study was conducted as a randomized controlled trial to evaluate the efficacy of the ShotBlocker device in reducing pain associated with IMI, a procedure frequently performed in emergency departments. Clinical Trials were registered prior to the study (NCT06624761). Ethical approval and institutional permission for the study were obtained (Toros University, Date: 07.06.2024, Approval No: 6/11). Participants were informed of their right to withdraw at any time prior to the study. Participants were informed about their group allocations after the completion of the study. Additionally, ShotBlocker intervention was offered to those in the control group if they wished.

Sample and participants

Based on a significance level (α) of 0.01, an effect size of 1.583, and a statistical power of 99% in G*Power statistical software, it was determined that a minimum of 25 participants per group was required. Considering the 95% confidence interval and the possibility of participant attrition, the planned sample size was increased to 30 participants per group. A total of 80 participants were included in the study. This expanded sample size resulted

in an estimated statistical power of approximately 99.7%, indicating that the observed differences were likely to be statistically significant and the results were highly reliable. Before participation, all individuals were informed about the study and their verbal and written consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria for both groups were as follows: patients aged 18 years and over who spoke Turkish, who applied to the emergency department for prescription drug use or who would be administered diclofenac sodium or metamizole sodium as IMI upon the request of the emergency department physician, and who signed the informed consent form.

Exclusion criteria for both groups included: pregnancy, presence of a psychiatric disorder, admission to the red zone of the emergency department, presence of confusion, secondary injury or infection at the injection site, prior injection to the same site within the last 24 hours, refusal or failure to sign the informed consent form, and regular use of ShotBlocker during previous injections.

Randomization

Participants were randomly assigned to either the intervention or control groups by an independent researcher using a randomization program. The randomization process is presented in Figure 1. Group assignment was conducted using a sealed, opaque envelope method. Envelopes containing group allocations were thoroughly shuffled, and one envelope was randomly selected for each participant, resulting in Group 2 being assigned to the intervention group and Group 1 to the control group. Participants were randomized under double-blind conditions, with neither the participants nor the researchers aware of group assignments during the allocation process. All results were analyzed at baseline and immediately after treatment by an expert who was not involved in the study.

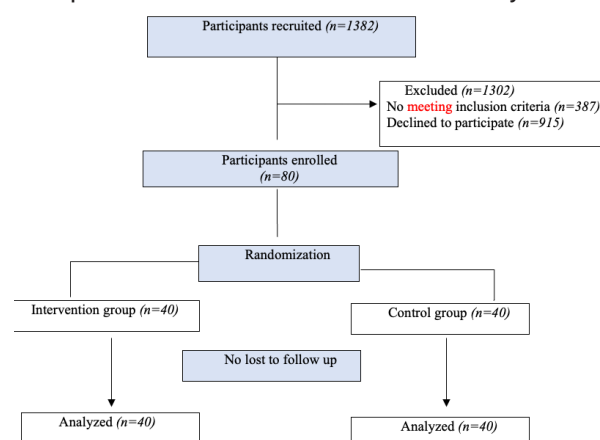


Figure 1. Consort diagram of the research

Intervention

The application steps are as follows:

Step 1: Preliminary Preparation Process

Preliminary discussions were held with nurses who were not participating in the study and who worked in the emergency department before the application began,

and detailed information was provided about the purpose, content and assessment tools to be used. The nurses were told that the ShotBlocker would be used in patients who met the research criteria and who would receive intramuscular diclofenac sodium and metamizole sodium in the ventrogluteal region, and that data would be collected from these patients. In this way, physicians were informed and prepared for the application process.

Step 2: Participant Information and Consent

The purpose of the study and the implementation procedures were explained to the participants in detail. Both verbal and written informed consent was obtained from the participants. The voluntary nature of the study and the ethical rules were taken as a basis.

Step 3: Visual Analogue Scale (VAS) Application to the Intervention Group

Pain intensity was measured using the VAS approximately two minutes after completion of the IMI in the ShotBlocker group. Since there is no direct source in the literature regarding timing, this time interval was determined by the researchers to ensure that the effect of the drug is clearly felt after the injection and to allow the patient to prepare herself before the evaluation.

Step 4: VAS Application to the Control Group

Similarly, the VAS was applied to subjects in the control group who were administered diclofenac sodium and metamizole sodium as IMI to the ventrogluteal region without using the ShotBlocker and who met the research criteria.

Measurements

Descriptive characteristics of the participants such as age, gender, income status, Body Mass Index (BMI) and type of medication used were collected using the Personal and Medication Information Form.

The pain perceived by the participants was measured with the VAS. In this scale, there is a line at one end of the ruler where there is no pain (zero) and a line at the other end where there is the most severe pain (10 cm). The person indicates their pain by marking a number from 1 to 10. On the VAS, 0-4.4 cm indicates mild pain, 4.5-7.4 cm indicates moderate pain, and 7.5-10 cm indicates severe pain (18,19).

Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). In descriptive statistics, frequency (n) and percentage (%) were used for categorical variables, and mean±standard deviation was used for continuous variables. Shapiro-Wilk test and Levene test were used to test the assumptions of normal distribution and homogeneity of variances, respectively. The t-test for independent samples was used for comparisons between two independent groups that fulfil these assumptions. In cases where more than two independent groups were involved, a one-factorial analysis of variance was performed. When significant differences were observed, Bonferroni post-hoc correction was applied

to determine specific group differences. For all analyses, p-values ≤.05 were considered statistically significant.

RESULTS

A total of 80 people were included in the study and it was determined that the genders were equal in the intervention and control groups. The mean age of the participants in the intervention group was determined to be 42.20±14.60, and the mean age of the participants in the control group was determined to be 47.00±15.10. In addition, it was determined that the mean BMI of the participants in the intervention group was 25.30±4.00, while the mean BMI of the participants in the control group was 26.10±3.60. Table 1 shows some sociodemographic characteristics of the participants in the intervention and control groups.

The comparison of the type of medication administered and the previous administration status of the participants according to the groups is shown in Figure 2. It was determined that more than half of the participants in the intervention group and the control group received diclofenac sodium. In addition, it was determined that all of the participants in both groups had previously been administered one of these drugs.

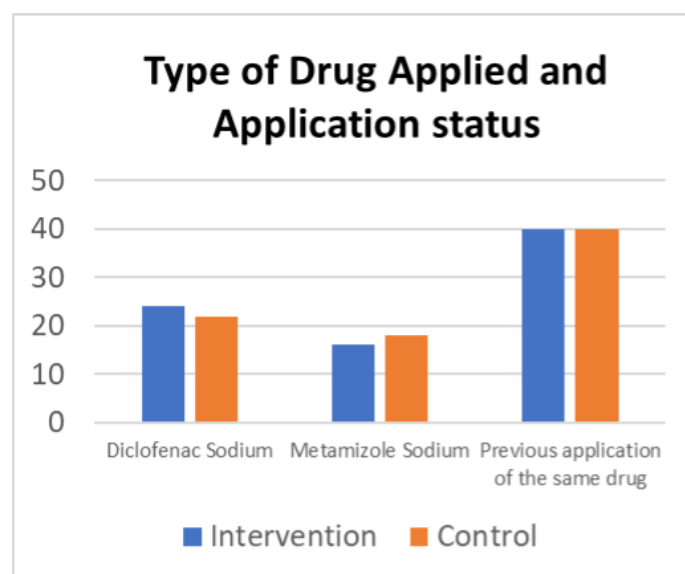


Figure 2. Comparison of the type of drug administered and previous administration status according to the groups

Table 2 presents the comparison of participants' mean VAS scores by group. The mean VAS scores of the participants before the intervention were similar in both the intervention and control groups and did not differ statistically significantly from each other. However, analysing the pain scores after the injection revealed a statistically significant difference between the groups, with the control group reporting higher mean pain scores ($p < .05$).

When the pre- and post-intervention mean pain scores of the intervention group were analyzed based on variables such as gender, education level, income status, and type of medication administered, the differences were found to be statistically significant ($p < .05$). Table 3 illustrates the comparison of participants' mean VAS scores according to selected characteristics within each group.

Table 1. Sociodemographic characteristics of participants by group (n=80)

Characteristics	Intervention group (n=40)		Control group (n=40)	
	M±SD		M±SD	
Age	42.20±14.60		47.00±15.10	
BMI	25.30±4.00		26.10±3.60	
	n	%	n	%
Gender				
Female	20	25.0	20	25.0
Male	20	25.0	20	25.0
Level of education				
Literate	4	10.0	6	15.0
Primary school graduate	3	7.5	6	15.0
Secondary school graduate	8	20.0	6	15.0
High school graduate	16	40.0	14	35.0
University graduate	9	22.5	8	20.0
Income status				
Income less than expenditure	20	50.0	17	42.5
Income equals expenditure	20	50.0	23	57.5
Income more than expenditure	0	0	0	0

BMI: body mass index, M: mean, SD: standart deviation, n: number, %: percentage

Table 2. Comparison of participants' mean Visual Analogue Scale scores by group (n=80)

Measurement time	Intervention group (n=40)		Control group (n=40)		*p
	M±SD	Minimum-maximum	M±SD	Minimum-maximum	
VAS					
Previous pain experience	5.82±1.92	2-10	5.55±1.60	2-9	.489
Experience of pain after drug administration	3.67±1.91	1-7	4.60±2.08	1-9	.042
**p		.000		.000	

* Independent sample t test, **Dependent sample t test, M: mean, SD: standart deviation, VAS: Visual Analogue Scale, p values≤0.05

Table 3. Comparison of participants' mean Visual Analog Scale Scores by characteristics and medication type (n=80)

Measurement times	Intervention group (n=40)			Control group (n=40)		
	Previous pain experience	Pain experience after shotblocker+ drug administration		Previous pain experience	Pain experience after drug administration	
	M±SD	M±SD	*p	M±SD	M±SD	*p
Gender						
Female	6.35±1.95	3.75±1.68	.000	6.05±1.60	5.30±1.92	.028
Male	5.60±1.78	3.60±2.16	.000	5.05±1.46	3.90±2.04	.001
**p	.084	.808		.047	.032	
Level of education						
Literate ¹	5.5±1.91	3.50±2.38	.016	7.17±1.47	6.17±1.47	.203
Primary school graduate ²	4.67±1.15	2.33±0.58	.020	6.17±1.94	6.17±2.32	1.000
Secondary school graduate ³	6.13±2.59	3.88±2.17	.003	4.33±1.21	4.17±1.94	.741
High school graduate ⁴	5.81±1.68	3.69±1.99	.000	5.43±1.02	4.43±1.40	.002
University graduate ⁵	6.11±2.09	4.00±1.80	.002	5.0±1.69	2.88±2.17	.002
***p	.825	.781		.014, 1>3	.007, 1>5	
Income status						
Income less than expenditure	5.70±1.89	3.60±1.81	.000	5.29±1.35	4.58±2.06	.041
Income equals expenditure	5.95±1.98	3.75±2.04	.000	5.73±1.76	4.60±2.14	.001
**p	.686	.808		.392	.976	
Type of drug						
Diclofenac sodium	5.33±1.78	3.75±1.68	.000	5.50±1.60	5.30±1.92	.090
Metamizole sodium	6.56±1.93	3.60±2.16	.000	5.59±1.65	3.90±2.04	.020
**p	.510	.040		.860	.574	

*Independent sample t test (between groups), **Dependent sample t test (Within groups), ***One-way analysis of variance, M: mean, SD: standart deviation, VAS: Visual Analogue Scale, p values≤0.05

DISCUSSION

IMI is frequently used by nurses in clinical practice and injection pain is one of the most common problems encountered in this practice (20). Although the level of this pain varies according to the content of the drug, the rate of administration and individual factors, it may also be related to the techniques used during injection administration. In fact, the application area, needle size, injection speed and the tools used are the determining factors in injection pain (21). Therefore, in this study, it was aimed to determine the effect of ShotBlocker on IMI pain in adult patients undergoing IMI.

In our study, the intervention and control groups exhibited similar baseline pain experiences. The group using ShotBlocker during injection showed significantly lower mean pain scores compared to the control group. Similarly, previous studies have reported that ShotBlocker effectively reduces injection pain in pediatric patients (16,22). In those studies, children in the ShotBlocker group reported lower pain scores during IMI compared to both cold application and control groups, with statistically significant differences. Findings from various studies conducted across different years and age groups further support our results (23-25). The underlying mechanism of this effect can be attributed to the gate control theory, which suggests that non-painful physical stimulation—such as that provided by ShotBlocker's contact points—can inhibit the transmission of pain signals and thus reduce the perception of needle-related pain (14,26). These findings highlight the practical relevance of the theory in clinical pain management.

In our study, when the pain scores of both groups were compared according to gender, it was found that the difference between them was significant among themselves and between the groups according to the same gender. In addition, it was observed that this difference between men and women in the intervention group was not significant before and after the intervention. The results of the study conducted by Bilge et al. (2019) supported our research findings and no significant difference was observed in VAS scores according to gender between the intervention groups (27). Our results show that Shotblocker application decreased pain in both groups and gender (Table 3). This finding suggests that not only biological but also psychosocial aspects of injection pain are important. Women in particular may have higher hormonal, psychological, and sensory sensitivities, which may affect pain perception (28). It is an important and striking finding in terms of showing that pain perception before and after the application varies according to gender (Table 3). Because sex hormones affect pain responses (29). A 2002 study highlighted that women experience more pain than men and that women have a lower pain threshold in experimental pain studies (30). However, gender-based interpretations of pain should be approached holistically, taking into account not only physiological but also cognitive, emotional, and sociocultural factors.

In our study, when the pain averages of the participants in both groups were analysed according to the type of drug administered, it was found that the mean previous

pain experience of the participants in the intervention and control groups were similar, while the mean pain experience of the participants taking metamizole sodium was higher. In the intervention group, it was determined that the mean pain in the metamizole sodium group decreased more than the diclofenac group after Shotblocker and the difference between them was significant according to the type of drug. This situation can be related to the fact that the pain caused by the damage left in the tissue due to the chemical structure of the drug depends on the way it is perceived by the patient.

In the control group, the decrease in the mean pain according to the type of drug and the significant difference between them may be related to the previous experience of the individuals about the application of this drug. However, this experience may not give the same result in all groups. In addition, the effects of Shotblocker on pain should not be ignored. In support of our study, Çelik and Khorshid (2015) investigated the effectiveness of Shotblocker on diclofenac and found that the average pain of the intervention group decreased compared to the control and control group (31). When the literature was examined, no study comparing the efficacy of Shotblocker in these two drug types was found. This situation reveals the originality of our study and provides a new perspective that can contribute to clinical practice.

Limitations

This study has several limitations. First, the study was conducted in the emergency department of a single state health institution on intramuscular pain. This may limit the generalizability of the findings to different institutions or different clinical settings. In addition, the study focused only on post-injection pain and other possible outcome variables (such as injection anxiety) were not assessed. In addition, pain assessment was performed only by self-report method (VAS) and no other assessment was used.

CONCLUSION

In conclusion, IMI are among the most painful procedures, regardless of the demographic characteristics of the individuals and the type of drug used. In this context, the management of pain that occurs during the injection is an important part of care. Nurses are expected to use appropriate injection technique, assess pain and use non-pharmacological methods. In this study, the use of ShotBlocker, a non-pharmacological intervention, was shown to reduce injection pain in adults. ShotBlocker's mechanism of action, based on the "gate control theory", suppresses the perception of pain that may occur during needle insertion through the painless physical stimulation it produces prior to injection. Our research shows that this effect is significant in relation to both gender and drug type. The fact that the ShotBlocker is particularly effective for painful injections such as metamizole and diclofenac speaks in favour of the applicability of the method in adults.

According to our research results; ShotBlocker is recommended to be integrated into nursing practices as a cost-effective, easy-to-use and reliable non-pharmacological method. However, in order to ensure

effective application in clinical practice, nursing staff should first be adequately informed and trained about its use. This recommendation is in line with the guidelines of the Registered Nurses' Association of Ontario (32), which emphasize the use of non-pharmacological methods—such as tactile stimulation and distraction techniques—for pain management during procedures like injections. Additionally, future studies are needed to strengthen the evidence base in different age groups, individuals with different clinical diagnoses (such as cancer pain), and with variables such as different injection sites. This will increase the generalizability and clinical applicability of the method. Additionally, future studies are needed to strengthen the evidence base in different age groups, individuals with different clinical diagnoses (such as cancer pain), and with variables such as different injection sites. This will increase the generalizability and clinical applicability of the method.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: Ethical approval and institutional permission for the study were obtained (Toros University, Date: 07.06.2024, Approval No: 6/11).

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Clinical Outcomes of Hyaluronic Acid–Based Scaffold Augmentation in Microfracture Treatment for Focal Osteochondral Defects in The Knee: A Retrospective Comparative Study

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Abstract

Aim: Microfracture is a common, cost-effective treatment for focal osteochondral defects (FCDs) of the knee. However, it often results in fibrocartilage with poor biomechanical properties. Hyaluronic acid–based biodegradable scaffolds like Hyalofast® have been developed to enhance cartilage regeneration and improve outcomes.

Material and Method: This retrospective study included patients with knee FCDs smaller than 3 cm², treated between 2015 and 2018. Two treatment groups were compared: microfracture alone versus microfracture combined with a hyaluronic acid–based scaffold. Clinical outcomes were assessed using Visual Analog Scale (VAS), International Knee Documentation Committee (IKDC), and Knee Injury and Osteoarthritis Outcome (KOOS) scores preoperatively and at 6 months postoperatively.

Results: Both groups showed statistically significant improvements in all clinical scores after treatment ($p < 0.001$). Although postoperative VAS and KOOS scores did not differ significantly between groups, the scaffold-augmented group achieved significantly higher IKDC scores compared to the microfracture-only group (66.35 ± 6.00 vs. 62.08 ± 8.51 , $p = 0.04$).

Conclusion: These findings suggest that while microfracture remains a valuable primary treatment for focal cartilage defects, scaffold augmentation may confer an additional functional benefit. Further prospective studies with long-term follow-up are warranted to confirm the clinical durability of scaffold-assisted cartilage repair strategies.

Keywords: Cartilage, knee joint, osteochondral allograft transplantation, hyaluronic acid, tissue scaffolds

INTRODUCTION

The regenerative capacity of articular cartilage is limited; therefore, cartilage lesions are often progressive and eventually affect the subchondral bone (1). Chondral and subchondral cartilage (osteochondral) lesions of the knee joint are common problems that can seriously affect the quality of life and mobility of individuals (2). When such lesions are not treated timely and appropriately, they can progress and lead to permanent joint diseases such as osteoarthritis (OA) (3). OA is a major public health problem that negatively affects not only individuals but also the health care system and labor productivity. The self-renewal capacity of articular cartilage is extremely limited; therefore, there is a growing need for effective treatment methods to repair cartilage damage. There are many treatment modalities for cartilage injuries, ranging from conservative approaches to invasive surgical methods

(4). However, none of these treatment modalities has so far been able to fully restore healthy and mature cartilage tissue (5). Despite this, microfracture procedures stand out due to their practical application, high accessibility and favorable clinical outcomes. Numerous treatment models in which microfracture is used in combination with various bioengineering approaches such as scaffolds have been investigated in the literature (6,7).

Microfracture, one of the treatment options used for this purpose, is a low-cost and practical procedure that can be performed arthroscopically (8). In this technique, small holes are drilled into the subchondral bone, allowing stem cells from the bone marrow to reach the damaged area and form a new cartilage-like tissue (5). However, this tissue is not as durable as the original hyaline cartilage and may deteriorate over time. Therefore, the long-term success of microfracture may be limited (9).

CITATION

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Hyaluronic acid-based bioabsorbable scaffolds (e.g. Hyalofast®), when used in combination with microfracture, can promote healing and contribute to the formation of a more durable and long-lasting cartilage tissue (10). These constructs can be placed arthroscopically or intra-articularly through small surgical incisions (11). However, their use is not widespread due to high costs, limited clinical data, and reservations about their economic effectiveness (12).

In this study, we retrospectively evaluated how microfracture treatment in patients with limited focal osteochondral defects (FCD) in the knee joint affects clinical and functional outcomes when used in combination with a hyaluronic acid-based bioabsorbable scaffold (Hyalofast®) compared to patients with microfracture alone. The size threshold of 3 cm² was selected based on prior evidence indicating that microfracture yields optimal outcomes in lesions smaller than 2.5–3 cm², whereas larger lesions are more appropriately treated with reconstructive techniques such as autologous chondrocyte implantation or mosaicplasty (12,13).

MATERIAL AND METHOD

In this retrospective cohort study, 49 patients with focal osteochondral defects below 3 cm² (Outerbridge grade 3–4) in the knee were treated with either microfracture combined with Hyalofast® scaffold implantation (Anika Therapeutics, Bedford, MA, USA) or microfracture alone. All procedures were performed at a single orthopedic center between 2015 and 2018 by the same surgical team. Patients in the microfracture-alone group were treated arthroscopically. In the scaffold group, the Hyalofast® membrane was cut to match the defect size and implanted via a mini-arthrotomy. Following implantation, approximately 3–5 mL of the patient's autologous whole blood was gently applied over the scaffold to promote adhesion and biological healing (Figure 1). No platelet-rich plasma (PRP) or chemical activation agents such as thrombin or calcium chloride were used. The scaffold was allowed to stabilize in the joint for a few minutes before closure to ensure adequate fixation. In patients without scaffold application, this option was not pursued due to limited access to medical supplies.

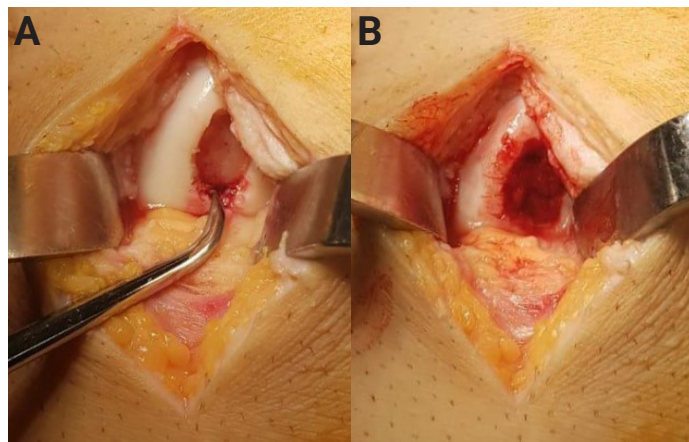


Figure 1. A. Macroscopic view of the focal chondral defect (FCD) area on the femoral condyle exposed via mini-arthrotomy; B. Application of the hyaluronic acid-based biological scaffold over the defect and its stabilization using the patient's autologous blood

A similar rehabilitation protocol was applied to all patients after surgery. Patients were not loaded for the first 6 weeks postoperatively; passive and active assisted exercises were started to maintain knee range of motion during this period. After the sixth week, tolerable weight bearing was allowed and exercises to increase quadriceps muscle strength were continued. The physical therapy process lasted an average of 12 weeks in total and all patients were followed up under the control of a physical therapist.

Patients who had undergone previous surgical intervention on the same knee, who underwent simultaneous different interventions, who experienced postoperative complications, who had incomplete clinical or imaging data, who were followed up at an external center, and who had systemic rheumatologic or neuromuscular diseases were excluded from the study. Visual Analog Scale (VAS), International Knee Documentation Committee Score (IKDC), and Knee Injury and Osteoarthritis Outcome Score (KOOS) recorded preoperatively and at 6 months postoperatively were analyzed retrospectively in patients selected according to the inclusion and exclusion criteria. All data were obtained from the hospital information management system and archival records. This study was approved by Düzce University Clinical Research Ethics Committee (Approval No: 2025/145, Date: 26.05.2025), and was conducted in accordance with the principles of the Declaration of Helsinki. As this was a retrospective study, the requirement for informed consent was waived by the ethics committee.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Continuous variables were expressed as mean±SD, and categorical variables as counts and percentages. Normality was tested with the Shapiro–Wilk test. Within-group comparisons were made using paired t-tests, and between-group comparisons with independent t-tests. Chi-square or Fisher's exact tests were used for categorical variables. A p-value <0.05 was considered significant.

RESULTS

A total of 49 patients were included in the study, with 26 treated using microfracture alone and 23 treated with microfracture combined with a hyaluronic acid-based scaffold. The mean age was 50.81±8.46 years in the microfracture group and 50.57±9.75 years in the scaffold group (p=0.92). Regarding cartilage lesion severity, only patients with Outerbridge grade 3 or 4 defects were included. In the microfracture group, 20 patients (76.9%) had grade 3 lesions and 6 (23.1%) had grade 4; in the scaffold group, 15 patients (65.2%) had grade 3 lesions and 8 (34.8%) had grade 4. There was no statistically significant difference in Outerbridge grade distribution between the groups (p=0.55), indicating similar baseline lesion severity. There were no statistically significant differences between the groups in terms of age or Outerbridge grade at baseline, indicating that the groups were comparable before treatment.

In both treatment groups, statistically significant improvements were observed between the preoperative and postoperative values for all outcome measures. In the microfracture group, mean VAS scores decreased from 6.00 ± 0.94 to 2.96 ± 1.18 ($p<0.001$), IKDC scores increased from 41.65 ± 8.12 to 62.08 ± 8.51 ($p<0.001$), and KOOS scores increased from 53.77 ± 7.40 to 73.31 ± 8.54 ($p<0.001$).

Similarly, in the microfracture + scaffold group, mean VAS scores decreased from 6.78 ± 0.85 to 3.26 ± 1.14 ($p<0.001$), IKDC scores increased from 47.74 ± 10.87 to 66.35 ± 6.00 ($p<0.001$), and KOOS scores increased from 54.04 ± 6.41 to 74.17 ± 5.77 ($p<0.001$). These findings demonstrate that both treatment modalities provided significant reductions in pain and improvements in knee function (Table 1).

Table 1. Preoperative and postoperative clinical outcome scores within groups				
Score	Group	Preoperative (Mean±SD)	Postoperative (Mean±SD)	p-value
VAS	Microfracture	6.00±0.94	2.96±1.18	<0.001
	Microfracture+Scaffold	6.78±0.85	3.26±1.14	<0.001
IKDC	Microfracture	41.65±8.12	62.08±8.51	<0.001
	Microfracture+Scaffold	47.74±10.87	66.35±6.00	<0.001
KOOS	Microfracture	53.77±7.40	73.31±8.54	<0.001
	Microfracture+Scaffold	54.04±6.41	74.17±5.77	<0.001
VAS: Visual Analog Scale, IKDC: International Knee Documentation Committee Score, KOOS: Knee Injury and Osteoarthritis Outcome Score, SD: Standard Deviation				

When comparing postoperative outcomes between groups, no statistically significant differences were observed in VAS scores (2.96 ± 1.18 vs. 3.26 ± 1.14 , $p=0.37$) or KOOS scores (73.31 ± 8.54 vs. 74.17 ± 5.77 , $p=0.67$). However, the postoperative IKDC score was significantly higher in the microfracture + scaffold group compared to the microfracture-only group (66.35 ± 6.00 vs. 62.08 ± 8.51 ,

$p=0.04$), indicating a potential advantage in functional recovery (Table 2).

Overall, both treatment strategies provided meaningful clinical improvements in pain and knee function; however, the addition of a hyaluronic acid-based scaffold may offer a modest advantage in terms of postoperative functional recovery.

Table 2. Comparison of postoperative clinical scores between treatment groups			
Score	Postoperative Mean±SD (Microfracture)	Postoperative Mean±SD (Microfracture+Scaffold)	p-value
VAS	2.96±1.18	3.26±1.14	0.37
IKDC	62.08±8.51	66.35±6.00	0.04
KOOS	73.31±8.54	74.17±5.77	0.67
VAS: Visual Analog Scale, IKDC: International Knee Documentation Committee Score, KOOS: Knee Injury and Osteoarthritis Outcome Score, SD: Standard Deviation			

DISCUSSION

Microfracture is a widely used, low-cost, and biologically based method for the treatment of FCD in the knee joint. This study aimed to investigate whether scaffold-supported treatment provides an additional advantage by comparing the clinical results of patients who received microfracture treatment alone with those who received Hyalofast® scaffold in addition to microfracture. Our findings show that both methods provide clinically significant improvement, while the addition of scaffold does not provide a statistically significant superiority on the results.

Microfracture technique is currently accepted as the gold standard treatment for lesions $<2.5\text{ cm}^2$ (13). In this method, the subchondral bone plate is punctured, allowing the mesenchymal stem cell-rich bone marrow content to migrate to the defect area, and the superclot formed provides a biological basis for cartilage matrix formation (14).

This method has long been preferred as the first step in the treatment of patients with FCD in the knee (15). Hyalofast is a biodegradable, nonwoven polymer produced from hyaluronic acid benzyl ester (16). In the biodegradation process of hyalofast, the main product becomes hyaluronan again (17). Thanks to this structural feature, Scaffold acts as a framework for cartilage tissue and has been widely used in clinical applications in recent years. In this study, we used Hyalofast® scaffold to provide structural support to the defect area and to enhance biological repair by applying it with the patient's own blood.

There are many studies investigating the effect of the combination of microfracture and scaffold on clinical outcomes. Bong et al. reported that the application of chitosan-based scaffold with microfracture increased KOOS scores from 58.4 to 80.9 and Lysholm scores from 57.3 to 83.1 (18). Similarly, De Marziani and colleagues showed that scaffold-assisted microfracture treatment resulted in significant improvements in IKDC scores from 46.3 to 70.1, and in KOOS subscales of pain (87.5),

symptoms (80.5), activities of daily living (88.3), sports/recreation (67.7) and quality of life (65.6) (19). On the other hand, Olivos et al. reported that microfracture led to lower Lysholm (75) and IKDC (61.8) scores compared to matrix-induced autologous chondrocyte implantation (MACI) (20). Altschuler et al. reported that aragonite-based scaffold resulted in a more significant increase in KOOS and IKDC scores compared to microfracture; IKDC scores increased by 24.0 at 6 months, 32.5 at 12 months, 38.1 at 18 months and 43.0 at 24 months (21). However, Wang et al. found no statistically significant difference in IKDC scores between microfracture and biphasic scaffold applications (22). Similarly, in our study, significant postoperative improvement was observed in Lysholm, IKDC and VAS scores in both groups, but a statistically significant difference between the groups was found only in IKDC scores ($p=0.04$).

Experimental studies to increase the regenerative capacity of scaffold application are remarkable. Li et al. demonstrated that PRP (platelet-rich plasma)-enriched hybrid polysaccharide scaffold improved the mechanical strength and histological quality of newly formed cartilage tissue by enhancing the sustained release of growth factors and stem cell attraction (23). Lu et al. reported that collagen scaffold enriched with solubilized cartilage extracellular matrix (ECM) significantly enhanced the recruitment and chondrogenic differentiation of mesenchymal stem cells, promoting hyaline-like cartilage formation and subchondral bone healing (24). Liu et al. stated that bionic cartilage acellular matrix microspheres (BCAMM) scaffolds, obtained at different developmental stages, provide biological advantages specific to different tissue types and therefore biofunctional scaffold design is an effective strategy to enhance cartilage regeneration (25). In a sheep model study, Peng et al. demonstrated that human articular cartilage-derived ECM scaffold applied in combination with microfracture improved the repair of cartilage defects with higher macroscopic, histologic, and biomechanical scores compared to microfracture alone (26). In our study, we think that the reason for the higher IKDC scores of the scaffolded patients is the effect of the treatment on cartilage formation.

In conclusion, this study shows that microfracture treatment is clinically effective, especially in FCD lesions <3 cm, while scaffold support, although it theoretically offers regenerative advantages, it did not show a statistically significant superiority in short-term clinical outcomes. The use of scaffolds in clinical practice should be evaluated in conjunction with patient selection, lesion characteristics, biomechanical integration of the scaffold, and long-term follow-up data. Prospective and long-term studies with larger samples will contribute to reaching clearer conclusions on this issue.

This study has several limitations. First, the retrospective design may introduce selection bias and limits the ability

to establish causal relationships. Second, the relatively small sample size and single-center setting reduce the generalizability of the findings. Third, the follow-up period of 6 months is relatively short and does not allow for assessment of long-term outcomes such as cartilage durability and reoperation rates. Therefore, further prospective studies with larger cohorts and longer follow-up durations are needed to validate and expand upon these results.

CONCLUSION

This study demonstrated that the microfracture method alone provides significant clinical improvement in the treatment of focal cartilage defects <3 cm in the knee joint. Although the addition of Hyalofast® scaffold to microfracture treatment has the theoretical potential to promote tissue regeneration, it did not provide any additional advantage in terms of short-term clinical outcomes. Significant improvement in VAS, IKDC and KOOS scores was observed in both patient groups. These findings suggest that clinical decisions affecting the choice of scaffold application should be based not only on biological potential but also on patient profile, material access and cost. Future prospective studies with larger samples and long-term follow-up will more clearly demonstrate the clinical efficacy of scaffold-assisted treatments.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: This study was approved by Düzce University Clinical Research Ethics Committee (Approval No: 2025/145, Date: 26.05.2025), and was conducted in accordance with the principles of the Declaration of Helsinki. As this was a retrospective study, the requirement for informed consent was waived by the ethics committee.

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Structural and Chromosomal Abnormalities Associated With Clubfoot: A Cross-Sectional Analysis From a Tertiary Referral Center

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Abstract

Aim: Clubfoot, which may be associated with some chromosomal diseases or as a concomitant of congenital malformations, is one of the congenital anomalies that can be easily diagnosed prenatally by ultrasound. It occurs in 1 to 3 out of 1000 live newborns and is more common in males. In around half of cases, this malformation is bilateral.

Material and Method: This study was designed as a retrospective cross-sectional study in which 32,256 pregnant women admitted to the perinatology clinic of Ankara Etlik City Hospital between September 2022 and June 2025 were retrospectively examined and clinical, demographic and genetic analyzes, concomitant anomalies, decisions to terminate pregnancy and postnatal follow-up data of pregnant women diagnosed with clubfoot were evaluated.

Results: In 26 of 64 pregnancies (40%) the clubfoot was isolated, while in 38 (60%) other congenital anomalies were present at the same time. Chromosomal abnormalities (trisomy 13 and 18, triploidy, mosaic Turner syndrome) were found in five (16.6%) of 30 patients who underwent prenatal genetic diagnosis. In four of these cases, the pregnancy was terminated. In most of the isolated cases, no additional findings were detected on postnatal examination, and follow-up and treatment of these cases was performed by the orthopedic department. The most common associated system abnormality in complicated cases was central nervous system (CNS) abnormalities, followed by skeletal, and cardiovascular system abnormalities. Abnormalities of the gastrointestinal tract and urinary system were less frequently associated and were considered more incidental.

Conclusion: Clubfoot is an easily detectable finding on routine prenatal ultrasound examination; however, its clinical significance increases when it is associated with abnormalities of other organ systems. Therefore, all systems should be thoroughly examined before considering a case as an isolated clubfoot.

Keywords: Birth defects, clubfoot, congenital anomalies, pes equinovarus, talipes equinovarus

INTRODUCTION

Clubfoot is a congenital condition that can easily be diagnosed prenatally. While some cases occur in isolation, others may be associated with chromosomal abnormalities or various other congenital malformations. The incidence is around 1 to 3 per 1,000 live births and is more common in male infants. Almost half of the cases are bilateral (1,2). About 60% of cases can be diagnosed by prenatal sonographic examination. Advances in sonographic techniques, particularly the use of three-dimensional imaging, have improved the diagnostic accuracy of sonography (3-6). With improved diagnostic capabilities, families can be thoroughly informed about the prenatal diagnosis of clubfoot and counseled about concomitant anomalies (if present) and planning of treatment options

on a case-by-case basis. In addition, clubfoot can be associated with a variety of structural anomalies, including cleft lip and palate, micrognathia, congenital heart defects, hydrocephalus, myelomeningocele and various other malformations (7,8). The presence of associated chromosomal and/or congenital anomalies may influence the management and treatment options available, depending on the final diagnosis. Early parental counseling can be facilitated and therapeutic approaches can be adjusted accordingly. Patients may also be referred for karyotype analysis. Karyotyping can detect conditions such as triploidy, trisomy 13 and trisomy 18 at an earlier stage so that the option of termination of pregnancy can be considered. On the other hand, it should also be borne in mind that a clubfoot can be an early indicator of neural or musculoskeletal disorders.

CITATION

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In our study, we examined clubfoot cases referred to a tertiary care center that is easily accessible from different regions of the country. We also investigated the structural and chromosomal abnormalities associated with these cases. The present study from a tertiary center allowed a detailed analysis of incidence rates and patient outcomes.

MATERIAL AND METHOD

Study Design

This study was conducted in accordance with the principles of the Declaration of Helsinki. The clinical research ethics committee of the University of Health Sciences Ankara Etlik City Hospital approved the conduct, protocol, and procedures of the study (31.01.2024, AEŞH-BADEK-2024-009). All participants have given their informed consent to participate in the study. After approval, a retrospective review of the medical records and ultrasound reports of a total of 32,256 patients who presented to the perinatology clinic of Ankara Etlik City Hospital between September 2022 and June 2025 was conducted.

Characteristics of The Study Population, Diagnosis, Study Variables, and Data Collection

Gestational age was calculated from the first day of the last menstruation and confirmed by sonographic measurement of the crown-rump length (CRL). If the calculation included fractions of days, gestational age was rounded up or down to the nearest whole week. Obstetric sonographic examinations were performed using a GE Voluson S10 Expert ultrasound machine (General Electric Medical Systems, Milwaukee, WI, USA). The diagnosis of clubfoot was confirmed by a team of at least three physicians, including obstetricians with at least 10 years of experience and perinatologists with at least 5 years of clinical experience. The presence of concomitant anomalies was also confirmed by the same team. To reduce the likelihood of false-positive diagnoses due to fetal position or oligohydramnios, particularly in cases of suspected isolated clubfoot, patients were re-examined two weeks later.

During the period covered by the study, all cases diagnosed prenatally with fetal clubfoot were included in the study. Pregnant women with missing data were excluded. Further exclusion criteria were: maternal age under 18 years, women refusing to be examined in a multidisciplinary prenatal council, in case of diagnostic suspicion due to an uncertain and stable fetal position or oligohydramnios. The ultrasound diagnosis of clubfoot, other ultrasound findings including concomitant other structural defects, fetal biometry and other clinical features were recorded (Figure 1). In cases where genetic testing had been performed, the results of karyotype analysis were reviewed. In addition, information was collected on requests for termination of pregnancy and postnatal outcomes. To assess postnatal outcomes, the medical records of the newborns were reviewed and the necessary information was obtained either by reviewing

the medical records or by direct telephone contact with the patients.

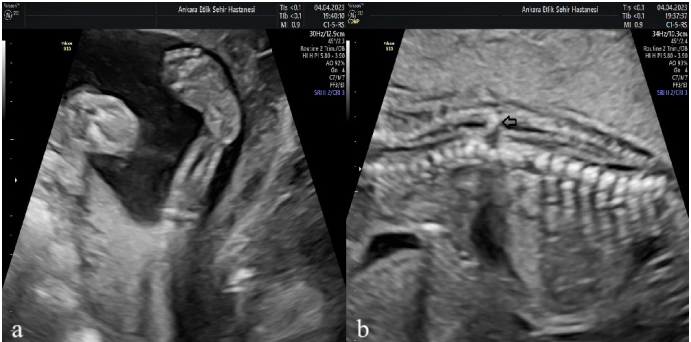


Figure 1. Images of a 32-year-old woman with: (a) fetal unilateral clubfoot and (b) diastematomyelia with bony spur (arrowhead)

Statistical Analysis

Due to the non-parametric distribution of the numerical data related to the demographic characteristics, the mean (median) and the minimum and maximum values were reported. Other data, including the results of the categorical variables, were given with frequency and percentage values.

RESULTS

A total of 64 pregnant women were prenatally diagnosed with fetal clubfoot during the study period. There were no exclusions due to missing data. The median age of the mothers was 28 years. In 46 of these women, both delivery and postnatal follow-up were performed in our perinatology clinic. Fourteen women (21%) were diagnosed with bilateral fetal clubfoot and three women (4%) had been conceived using assisted reproductive techniques. The median gestational age at diagnosis was 22 weeks.

Twenty-six women (40%) were found to have fetal isolated clubfoot on prenatal ultrasound, while 48 patients (60%) had additional congenital anomalies. Invasive prenatal testing was performed in 30 patients (47%) and chromosomal abnormalities were detected in five fetuses: Trisomy 18 in two cases, trisomy 13 in one case, triploidy in one case and mosaic Turner syndrome in one case. In four of these five cases with chromosomal abnormalities termination of pregnancy (TOP) were done. Although whole exome sequencing (WES) was recommended for several patients, the test was not performed for financial reasons and because the presence of multiple systemic abnormalities significantly limited fetal viability, leading to a recommendation for TOP.

Of the 26 isolated cases of fetal clubfoot, 10 were followed up at our center and no morphological findings suggestive of a syndrome or genetic disorder were noted on postnatal examination. These infants were managed and treated by the orthopedic department. Of the 48 patients with complex fetal congenital anomalies, 19 accepted the TOP recommendation. In four patients who refused the TOP recommendation, intrauterine fetal demise occurred during follow-up (Table 1).

Table 1. Demographic and clinical features of the cases			
Variable	Frequency	Details	Results
Maternal age	28 (22-34)		
Bilateral clubfoot	14 (21)		
ART	3 (4)	IVF (2), OI (1)	
GAAD (week)	22 (16-32)		
Isolated clubfoot	26 (40)		
Prenatal genetic testing	30 (47)	AC (28), PUBS (2)	
Chromosomal abnormalities	5 (7)	Trisomy 18 (2), Trisomy 13 (1), Triploidy (1), Mosaic Turner (1)	TOP (4)
Central nervous system	18 (28)	ACC (2), DCC (2), Iniencephaly (1), VM (8), NTD (8), lissencephaly (1)	TOP (12)
Musculoskeletal system	16 (25)	Tibia and/or fibula hypoplasia (3), calcaneus hypoplasia (1), clenched hands (8), caudal regression (2), bowing deformity (2)	TOP (2), IUFD (2)
Gastrointestinal system	4(6)	Liver calcifications (2), BA (1), mesenteric cyst (1)	Neonatal death (1)
Cardiovascular and respiratory systems	9 (14)	VSD (5), DORV (2), TOF (2), ASD (1), AC (1), PE (2)	TOP (5), IUFD (2)
Urogenital system	4 (6)	UTD (2), megacystis (2)	TOP (1)
AC: aortic coarctation, ACC: agenesis of the corpus callosum, ART: assisted reproductive technique, ASD: atrial septal defect, BA: biliary atresia, DCC: dgenesis of the corpus callosum, DORV: double-outlet right ventricle, GAAD: gestational age at diagnosis, IUFD: intrauterine fetal demise, IVF: in-vitro fertilization, NTD: neural tube defects, PE: pleural effusion, OI: ovulation induction, TOF: tetralogy of Fallot, TOP: termination of pregnancy, UTD: urinary tract dilatation, VM: ventriculomegaly, VSD: ventricular septal defect; Data are expressed as median (min-max) or number (percentage) where appropriate			

DISCUSSION

In our study, among the systemic abnormalities of the human body, fetal central nervous system (CNS) abnormalities were found to be most commonly associated with fetal clubfeet. We believe that CNS-related clubfoot cases are more commonly observed due to the long-term anatomic effects of these abnormalities and the crucial role of neurologic transmission in fetal movements. This finding is consistent with the literature and the results of Canto and colleagues (8). In general, patients in this group are more likely to require TOP. CNS abnormalities were followed by skeletal system abnormalities, which were observed in 25% of cases. Although this order is not entirely consistent with the literature, it can be attributed to the fact that we are a tertiary care center and a medical referral facility where several medical specialties work together simultaneously, resulting in a more selective patient population. After abnormalities of the skeletal system, abnormalities of the cardiovascular system were the third most common. Most patients in this group were also diagnosed with chromosomal or genetic syndromes through simultaneous testing. In cases where no TOP was performed, postnatal surgery was usually unavoidable.

On the other hand, patients with abnormalities of the gastrointestinal tract generally had a good prognosis and did not require surgical intervention. The coexistence of clubfoot with abnormalities in this system is often considered coincidental. In the current literature, there is no proven association between clubfoot and abnormalities of the gastrointestinal tract (9,10). In fetuses with abnormalities of the genitourinary system, the association with clubfoot is often attributed to fetal compression due to oligohydramnios or anhydramnios secondary to urinary tract obstruction. This theory is widely accepted as the coexistence of urogenital anomalies and clubfoot, similar

to the gastrointestinal tract, is not commonly found in the literature. Moreover, in agreement with previous studies, we observed that isolated cases of clubfoot have a better prognosis than complex cases.

Chromosomal abnormalities were diagnosed in five of the patients included in the study. In the cases in which detectable genetic disorders were investigated by chromosomal microarray, genetic conditions were found in 17.5% of the clubfoot cases with multiple anomalies, whereas a genetic disorder was found in only 3.9% of the isolated clubfoot cases (9). In our study, microarray analysis was not performed in patients diagnosed with complex clubfoot because of the severity of the associated abnormalities and for reasons of cost-effectiveness. Despite significant efforts to exclude false-positive cases, we are unable to determine the outcome of potential false-negative cases, primarily because our institution is a tertiary referral center. However, the false-positive rate among patients cared for and delivered at our center was 0. However, it is generally accepted that there is always some false-positive rate in studies of this type (9,11,12). Our low false-positive rate was achieved by rechecking the clubfoot diagnosis at each follow-up visit to ensure that the clubfoot was consistently detected and by excluding those cases where the finding was not confirmed. However, it should be noted that in some cases the clubfoot finding may regress during the course of pregnancy (7).

Our study has some limitations, mainly due to its retrospective nature. These limitations include the postnatal confirmation of clubfoot by several physicians, which may lead to variability, and the relatively low rate of karyotyping performed. In addition, due to the retrospective nature of the study, data on pathology examinations were limited, which may lead to selection bias due to participant attrition. The main strength of this study is that it was

conducted in a large reference hospital that uses the same algorithms for diagnosis, treatment and follow-up.

CONCLUSION

Clubfoot is a finding that can be detected during routine prenatal clinic visits, but its clinical significance increases when it is associated with abnormalities in other organ systems. Before classifying a case as an isolated clubfoot, a thorough examination of other systems should be performed. Referral of pregnant women with suspected fetal clubfoot to perinatologists for investigation of additional abnormalities and confirmation of diagnosis may be appropriate as part of clinical management guidelines. In addition, future multidisciplinary studies that include both false-positive and false-negative cases may help to avoid overemphasis on clubfoot.

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Investigation of Older Adults' Perspectives on Nutrition and Food Availability Processes with a Community-Based Approach

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Abstract

Aim: The aim of the study is to investigate the attitudes of older adults towards nutrition and food availability processes and to offer solutions with a community-based approach to these attitudes.

Material and Method: This qualitative study was conducted using a phenomenological design. Sixteen older adults (8 women and 8 men) aged 65-80 years participated in the study. Semi-structured in-depth interviews were conducted with the participants on an online platform. The data were analyzed using thematic analysis and presented in 3 themes (dietary preferences, attitudes towards food access and future expectations about nutrition) and 5 sub-themes (food consumption habits and food choice, attitudes towards food choice, attitudes towards food waste, attitudes towards food shopping).

Results: According to the findings of the study, the majority of the participants prepared meals at home, ate two meals a day and paid attention to consume vegetables, fruits and meat products on a weekly basis. However, it was concluded that economic inadequacies limit food purchasing power and food choices are mostly shaped by price-performance balance. Participants were sensitive about paying attention to the expiration date; however, knowledge-based behaviors such as label reading and sustainable packaging preference were found to be at a more limited level. Although conscious attitudes towards preventing food waste are widespread, it was stated that some products are given up due to budget constraints, despite acting in a planned manner during the shopping process. It was found that the main expectations of the participants regarding nutrition were concentrated on increasing their pensions, ensuring access to affordable food, and being able to consume more meat and meat products in particular.

Conclusion: This study found that older adults generally make informed food choices, but are forced to be price-oriented due to economic constraints, suggesting the need for community-based interventions in these areas.

Keywords: Older adults, nutrition attitudes, food access, food choice, community-based approach

INTRODUCTION

Older adult is a stage of life when individuals become vulnerable not only physiologically but also economically, socially and environmentally (1). Nutrition plays a direct role in the quality of life, capacity for independent living and general health status of older adults in maintaining a healthy life in this process (2). Nutrition is a fundamental factor that has a direct impact on individuals' quality of life, general health status and their capacity to live independently. However, the factors that determine how individuals eat are not limited to personal preferences (3). Numerous factors such as economic opportunities, food access conditions, food preferences, level of knowledge

and social support systems directly shape individuals' dietary habits (4). In recent years, the increase in food prices around the world has made it difficult to access many basic nutrients, especially protein-rich animal products, and has significantly affected the ability of individuals to purchase adequate nutrition (5). This situation is not only economic, but also combines with multifaceted factors such as physical ability, life loneliness, appetite status, access to information and shopping ability to create complex effects on individuals' food choices and consumption behaviors (6). In this framework, considering that a significant proportion of retired individuals in Turkey have an income below the minimum wage, it is foreseen that older adults may be

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in the risk group in terms of access to adequate and balanced nutrition (7). Consequently, approaches that focus only on individual preferences or behavior patterns are insufficient to explain the nutrition and food access problems of older adults in a holistic manner (8). Nutrition behaviors are shaped by the interaction of multilayered factors such as economic stability, social support networks, access to health services and food policies (9). This situation makes the need for multi-stakeholder and holistic community-based interventions that involve the responsibility and contribution of all segments of society, not just the individual, increasingly evident (10).

When the literature is reviewed, it is seen that studies on the nutritional status of older adults mostly focus on biomedical indicators such as energy intake, macro and micronutrient levels, anthropometric measurements and malnutrition risk (11,12). Studies examining older adults' perceptions of nutrition, its reflection on eating behaviors and factors in food choices are limited (13-15). To the best of our knowledge, there is no study in which the attitudes of older adults in the processes of nutrition and food selection are examined from the perspective of community-based approach through qualitative research method through their own views. Based on this, the aim of this study is to examine the attitudes of older adults in the processes of access to nutrition and food and to present community-based solution suggestions for these attitudes.

MATERIAL AND METHOD

Study Design

This study was planned within the framework of qualitative research method and phenomenology design. The study was conducted between November 2024 and April 2025 with older adults between the ages of 65-80. The research was carried out at the Faculty of Health Sciences, Trakya University. In the study, older adults' attitudes about their nutritional status and food choices were examined through semi-structured in-depth interviews. Through the interviews, qualitative data were obtained on older adults' perceptions and attitudes towards nutrition and food choices. The findings were analyzed and interpreted within the framework of a community-based approach. Approval for this study was obtained from Lokman Hekim University Scientific Research Ethics Committee on May 29, 2024 (Code: 2024145). Written informed consent was obtained from the participants and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. In the study design, the "Consolidated criteria for Reporting Qualitative (COREQ)" qualitative research guide used to report qualitative research was followed (16).

Participants

The study included community-dwelling older adults aged 65 to 80 years residing in the central districts of

Ankara, Hatay, Kayseri, and Mersin provinces. Individuals who did not understand or speak Turkish language, and older adults who had difficulty in cooperation or communication, and those with chronic diseases (cancer, rheumatologic, orthopedic, neurologic and cardiovascular) whose symptoms could not be controlled and negatively affected nutritional status were excluded from the study. A total of 16 participants were included in the study and these people were reached by snowball sampling method. In order to protect the confidentiality of the participants' identity information, each individual was assigned codes (pseudonyms) ranging from Participant (P)1 to P16.

Data Collection

Data on age, gender, height, weight, body mass index (BMI), proportion of income allocated to food expenditures and income level were collected. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Following these anthropometric data, semi-structured questions in the qualitative data collection form created within the scope of the research were used to understand in depth the participants' views on their nutritional status and attitudes towards food choice.

Qualitative Research Questions

The semi-structured interview form, which forms the basis of the qualitative data collection process, was developed in line with the information obtained from similar studies in the literature (9,17-19). In the first stage, a question pool of 35 questions was created to comprehensively meet the research purpose. Among these questions, those that were open-ended, non-leading and capable of revealing the nutritional status of older

adults and their attitudes towards food choices in depth were selected and a final semi-structured interview form consisting of 9 main questions was created. In order to evaluate the comprehensibility and applicability of the form, a pilot study was conducted with three older adults and it was concluded that the questions were clear, simple and appropriate for the purpose of the research in line with the feedback received from the participants. The semi-structured interview form consists of open-ended questions that aim to gain an in-depth understanding of older adults' experiences and perceptions of their nutritional status and their attitudes towards food choices. The questions were structured around content, particularly dietary routines, access to food, food choices, the effects of economic inadequacies on nutrition, and changes in dietary preferences. During the interviews, a flexible and exploratory approach was adopted so that participants could better explain their own experiences; follow-up questions such as "What do you think about this?", "Can you give an example?" and "Can you explain this situation a little more?" were used to deepen the interview. The semi-structured interview questions used in this study are shown in Table 1.

Table 1. Semi-structured interview questions

Question 1.	Can you give us information about your daily nutrition routine and meal habits?
Question 2.	Could you tell us about your food consumption and your criteria for choosing?
Question 3.	What do you think about your diet in general? Do you think it is sufficient and balanced?
Question 4.	How do you go about your food shopping process? Where do you shop and how often?
Question 5.	How do you use leftover food or food? Do you have any practices in your daily life to prevent food waste?
Question 6.	What are the factors that affect your choice when making food shopping decisions?
Question 7	How do you think your income level or economic situation affects your food choices or eating habits?
Question 8.	What kind of support do you think would be useful to facilitate your access to food?
Question 9.	What changes would you like to make or opportunities would you like to have in order to improve your eating habits in the future?

Data collection process

Within the scope of the research, data were collected through individual interviews with the participants using semi-structured interview method. Informed written consent was obtained from the participants before starting the interviews. Considering the accessibility and comfort of the participants, the interviews were conducted via teleconferencing over an online platform. All interviews were audio recorded with the permission of the participants.

All interviews were conducted by one researcher who was familiar with the research process; during the interviews, the other researcher participated online as an observer, but did not intervene. Each interview lasted approximately 20 to 30 minutes, depending on the participant's willingness to respond and the detail of the narrative. The data was considered saturated when meaningful recurrence of themes was observed, recruitment of new participants was discontinued and the study was terminated.

Data Transcription and Data Security

All audio-recorded interviews were transferred to a word file and recorded. The interview recordings were securely stored in an encrypted digital environment accessible only to the research team. The transcription process was verbatim, without disturbing the integrity of the individual's expression; pauses, emotional expressions and important emphases were also noted in the transcript. Thus, it was aimed to prevent loss of meaning in the thematic analysis process.

Regarding data security, pseudonyms (P1-P16) known only to the researchers were assigned to each individual to protect the confidentiality of the participants' identity information. In the process of sharing and storing the data in the digital environment, the principles of the Law on the Protection of Personal Data were followed and the ethics committee approval was obtained.

The Researcher Role and Bias Control

In this study, the fact that all interviews were conducted

by the same researcher ensured consistency in the interview language and approach. During the interview process with the participants, the researcher took care to avoid directing, to remain impartial and to create a safe environment in which the participants could freely express their statements. In order to minimize possible researcher biases, a double coder approach was adopted in the analysis process; the codes and themes obtained were also examined by a second researcher and finalized by mutual consensus. This method supported a more reliable and objective analysis of the data.

Data Analysis

The data collected in the study were analyzed in a way to complement each other in qualitative and quantitative aspects. Data on age, gender, height, weight, BMI and the proportion of budget allocated to food from income were analyzed using SPSS IBM 22 Software. These data were presented as mean and standard deviation. Qualitative data were obtained through semi-structured interviews with the participants, and the audio recordings were transcribed by the researchers after the interview and converted into written text. The thematic analysis method was used to analyze the data. In this context, the texts obtained were carefully read in line with the research questions and the expressions that carry a meaningful integrity within the data were coded; themes and sub-themes were formed by combining similar codes together. The coding process was carried out independently by two researchers and consistency between themes was ensured through comparative analysis. In the analysis process, direct participant statements were also included as quotations in order to reflect the richness of the content.

The data were analyzed using descriptive analysis method and the opinions of the older adults were grouped under 3 themes (nutritional preferences and beliefs, attitudes towards food access, and future expectations about nutrition) and 5 sub-themes (food consumption habits and food choice, attitudes towards food choice, attitudes towards food waste, and attitudes towards food

shopping): Findings are presented in tabular form and themes are supported by direct participant quotes.

RESULTS

Sixteen older adults (8 females, 8 males) participated in the study. Fourteen participants were married, while

two were single. Descriptive information about the older adults participating in the study is provided in Table 2.

The opinions of the older adults participating in the study were categorized into 3 themes: nutritional preferences and beliefs, attitudes in the process of accessing food, and future expectations about nutrition.

Table 2. Descriptive characteristics of the participants		
Older adults		
n=16		
Mean± SD		
Age (years)	67.53±4.66	
Height (cm)	161.66±6.84	
Weight (kg)	74.13±11.63	
BMI (kg/m²)	28.24±4.96	
Budget ratio allocated to food from income (%)	38.3±2.5	
	n	%
BMI classification		
18.5-24.99 (Normal weight)	2	12.5
25-29.99 (Overweight)	10	62.5
30 and above (Obese)	4	25
Monthly income		
Less than half the minimum wage	2	12.5
Between ½ and full minimum wage	7	43.75
Up to minimum wage	4	25
Between 1-1.5 times the minimum wage	3	18.75
n: number of people, %: percentage, SD: standard deviation, cm: centimetre, kg: kilogram, m²: metre square		

The theme of dietary preferences and beliefs was analyzed under two sub-themes: food consumption habits and food purchasing power. Under the sub-theme of food consumption habits, it was determined that the majority of the participants ate two meals a day (n=9), prepared their meals at home (n=14), consumed meat at least once a week (n=16) and consumed vegetables and fruits daily (n=14). It was also found that a small proportion of the participants preferred snacks such as sweets, chips, chocolate and biscuits (n=4) and more than half of the participants used sources such as books, internet, television and social media to obtain information about nutrition (n=9) (Table 3).

P-1: *We used to eat three meals a day, but now two meals are enough for us. We have a late breakfast and dinner. We try not to eat too late because I have a stomach disorder. We eat less, but we try to choose good and natural foods for these meals.*

P-2: *The prices of eating out are quite expensive, we don't prefer to eat out in these conditions, my wife and I usually eat at home.*

P-3: *The prices of food products have increased so much that we can't buy everything. Meat is very expensive, I used to use meat much more in my meals, but now I can't say*

that we consume it as much as before.

P-4: *We try to consume meat as much as we can, but the weight of meat is quite high, we used to consume more, now we try to consume it again by cutting back on other expenses.*

P-8: *We take care to eat healthy, so we try to consume fresh vegetables and fruit daily. We also do not consume chips and fizzy drinks, we take care to eat healthy foods.*

P-9: *We eat dessert, we love it, but we usually try to consume the desserts I make at home. I don't find sweets made outside very healthy and they are also expensive.*

Within the sub-theme of food choice, it was determined that most of the participants had difficulty in food intake compared to previous years (n=15), found their purchasing power insufficient (n=12), and made decisions based on the price-performance variable in their food preferences (n=9) (Table 3).

P-5: *I do not save on food, I save on other needs. Quality is therefore important to me and I eat the best quality food.*

P-10: *The content and quality of the food I eat is important to me, but in recent years I have found it difficult to buy the foods I want, so I now prefer products that are both affordable and of good quality.*

P-11: *In the past, we used to buy quality products and anything we wanted, but now our purchasing power has obviously decreased a lot, so I buy the most affordable products.*

Table 3. Older adults' views on dietary preferences			
Theme	Nutritional preferences and beliefs	Older adults n=16	
Sub-theme	Food consumption habits	n	%
Number of meals (2 meals)		9	56.25
Number of meals (3 meals)		7	43.75
Preparing meals at home		14	87.5
Eating out		2	12.5
Eat one of the meat (red, white) and fish products once a week.		16	100
More than 1 meat (red, white) and fish product per week		4	25
Consuming vegetables and fruits daily		14	87.5
Consumption of sweet products		7	43.75
Food consumption such as chips, chocolate, and fizzy drinks		4	25
Those who use sources of information such as books, the internet, TV and social media to obtain information about nutrition		9	56.25
Sub-theme	Food selection	n	%
Difficulty in food intake compared to previous years		15	93.75
Stating that there is insufficient food intake power		12	75
Giving priority to quality in food selection		4	25
When choosing food, do not prioritize price.		4	25
Deciding on price-performance variables in food selection		8	50
Shopping for food based on its content		9	56.25
Preferring more filling foods		4	25

n: number of people, %: percentage

The theme of the food access process attitude of the older adults participating in the study was examined within the scope of three sub-themes: food choice, food waste and food shopping attitude.

Within the framework of the food choice attitude sub-theme, it was determined that only less than half of the participants have the habit of reading food labels (n=7), whereas the majority pay attention to expiration dates (n=14), take care to consume seasonal products (n=14), prefer locally produced foods (n=12) and adopt the use of non-packaged products (n=6). It was determined that the number of those who prefer products with recyclable packaging is low (n=4) (Table 4).

P-5: *When I shop at the supermarket, I look at the label but I don't really read the ingredients; however, I definitely look at the expiration date and if the expiration date is close, I definitely don't buy that product.*

P-6: *As a family, we care about healthy eating, we have been shopping at the market for years and we choose the products ourselves, we do not buy any products or food that is not fresh.*

P-7: *When shopping at the market, I especially try to choose local products, as they are more affordable and seem safer to me because they are produced in our country.*

P-11: *Whenever possible, I prefer products without packaging; however, if I buy packaged products, I unfortunately do not pay much attention to whether they are recyclable or have paper packaging.*

Within the scope of the sub-theme of attitude towards food waste, it was determined that the majority of the participants prepared only the portions they could consume (n=15), did not waste during the preparation and consumption process (n=15), and used leftovers by transforming or storing them (n=15). It was also determined that almost all of the participants did not throw away food because they could not consume it (n=1) or it got stale (n=1) (Table 4).

P-12: *We definitely do not throw away food. We cook as much as we can eat, and if there is any leftover, we eat it the next day.*

P-14: *We never throw away leftover food; we either put it in the freezer or the fridge. Even if it gets stale, we heat it up and eat it. Even if we are not going to eat it, we give it to animals instead of throwing it away.*

Within the scope of the food shopping attitude sub-theme, it was determined that most of the participants prepared a list before shopping (n=14) and made planned shopping (n=14). Some of the participants stated that

they could not buy some products due to insufficient food purchasing power (n=12), had financial difficulties in shopping due to high prices (n=15) and therefore had to save money (n=12) (Table 4).

P-13: *I always make a list before going to the market, but I don't buy all the things I need anymore because some products are*

expensive. I buy some products when they are on sale.

P-16: *Frankly, I have a hard time buying the food products I want with my current income. I often can't afford certain products because the prices are too high for my income level. About 35% of my income goes to food, and it's hard for me to make ends meet with the rest of my budget.*

Table 4. Participants' attitudes towards food access			
Theme	Food access process attitude	Older adults n=16	
Sub-theme	Food choice attitude	n	%
Label reading		7	43.75
Food purchases by expiration date		14	87.5
Consumption of products that are in season		14	87.5
Preferring locally produced products		12	75
Prefer packaged products		6	37.5
Preferring recyclable packaging when purchasing packaged products		4	25
Sub-theme	Attitude towards food waste	n	%
Preparing portions to be consumed		15	93.75
Not wasting food during preparation or consumption		15	93.75
Transform/store leftovers		15	93.75
Food waste due to non-consumption		1	6.25
Throwing away food due to staleness		1	6.25
Demonstrate strategies, attitudes and behaviors to reduce waste		16	100
Sub-theme	Food shopping attitude	n	%
Preparing a shopping list		14	87.5
Planned shopping habit		14	87.5
Inability to purchase certain products due to insufficient purchasing power of food products		12	75
I have financial difficulties in my food shopping due to expensive prices		15	93.75
Those who have to save money due to lack of purchasing power in purchasing food products		12	75
n: number of people, %: percentage			

Within the scope of the theme of expectations regarding nutrition, a significant portion of the participants stated that they wanted to be able to consume more meat and meat products (n=13) and to be able to easily buy the foods they wanted (n=14). In addition, strong demands were expressed for increasing pensions to provide access to the foods they wanted (n=15), providing more affordable food for older adults (n=14), and providing food aid to the older adults in need (n=12) (Table 5).

P-9: *Frankly, we want to consume more meat, but with our current salary, we cannot afford to buy the amount of meat*

we want. We even have to save money when buying some foods other than meat.

P-13: *I can't say that my nutritional status is bad; but I would certainly like to be able to buy the foods I want more easily and to eat better. For this reason, I think that pensions should be increased.*

P-15: *I spend almost 40% of my salary on food. Since this rate is quite high, I have to cut back on my other needs. It is not easy to work at a job after this age; therefore, affordable or discounted food sales or food aid can be provided for older adults.*

Table 5. Future expectations regarding nutritional status and requirements in older adults			
Theme	Nutritional expectations	Older adults n=16	
		n	%
Ability to consume more meat and meat products		13	81.25
Desire to be able to consume the foods he/she wants		14	87.5
Increasing pensions so they can consume the food they want		15	93.75
Selling more affordable food to older adults		14	87.5
Providing food aid to the older adults		12	75
n: number of people, %: percentage			

DISCUSSION

This study qualitatively examined the dietary preferences, food access processes and nutritional expectations of older adults. Findings revealed that the majority of participants prepared meals at home, ate two meals a day, and consumed meat at least once a week and daily vegetables and fruits. However, it was observed that economic constraints significantly affected food intake, many participants had difficulty in purchasing food compared to the past and prioritized price-performance balance in food selection. Although positive behaviors such as paying attention to expiration dates and preferring seasonal and locally produced products were adopted in the food selection process, awareness on issues such as reading food labels and choosing sustainable packaging was low. In terms of preventing food waste, it was found that most of the participants exhibited a conscious attitude, utilized leftover food and developed strategies to reduce waste. Although planning behavior in food shopping was common, it was emphasized that due to lack of income, some products could not be purchased and savings had to be made. Expectations regarding nutrition focused on basic economic support needs such as more meat consumption, increased pensions, access to affordable food and food aid.

Food Consumption Habits Sub-Theme

Whitelock and colleagues stated that older adults prefer to prepare meals at home for both healthy nutrition and economic reasons (17). Zou et al. emphasized that the frequency of eating out decreases among older adults due to economic constraints and health concerns (20). Another study concluded that older adults have high awareness of using healthy foods (8). In our current study, it was found that most of the participants prepared meals at home, ate two meals a day, paid attention to vegetable and fruit consumption and had low consumption of snacks. Concerns about the cost and safety of eating out reinforce home cooking habits, suggesting the maintenance of traditional diets. However, the low number of daily meals may also be related to psychosocial factors such as decreased appetite with age, metabolic slowdown and loneliness.

In line with the community-based approach, seminars can be organized at the local level in cooperation with public health units for older adults to maintain healthy eating routines; individual nutrition counseling can be provided with a dietitian and individualized meal plans can be made. In addition, guided group activities that integrate eating out with social interaction can be planned from time to time to reduce social isolation and support healthy choices.

Food Intake Power Sub-Theme

Food purchasing power is considered a fundamental determinant that directly affects the right of older adults to adequate and balanced nutrition (9). Park and Kim

emphasized in their study that individuals find the price factor as decisive as health and food quality in their food choices, and that budget constraints are at the forefront in the shopping behaviors of individuals with fixed incomes in particular (21). A meta-analysis indicated that limited access to high-protein foods among low-income older adults may contribute to an increased risk of sarcopenia (22). According to the 2024 data of the Turkish Statistical Institute, the share of food and non-alcoholic beverage expenditure in total expenditure for all households was found to be 18% (23). Compared to previous years, most of the respondents reported that they had difficulty in purchasing food, found their purchasing power insufficient and prioritized the price-performance balance in food selection. This can be considered as one of the direct effects of food inflation. Considering price-performance balance in food selection shows that older adults act in line with their budgets, not only nutritional value. This finding is thought to indicate that the dietary behaviors of older adults are shaped under economic constraints.

To this end, within the scope of the community-based approach, nutrition awareness campaigns promoting low-cost but nutritious menus for the older adults can be organized in cooperation with local governments and social service units; special discount days for the older adults can be implemented in public markets. In addition, prioritizing protein sources (e.g. red/white meat, legume packages) in publicly supported food support programs would be an important step towards strengthening the purchasing power of older adults and increasing their access to adequate nutrition.

Food Choice Attitude Sub-Theme

Food choice behaviors are not limited to individual preferences, but are shaped by multifaceted factors such as knowledge level, perceptions and environmental factors (24). Karademir et al. emphasized that the information on food labels can positively affect consumer decisions; however, the effective use of this information is closely related to the individual's level of nutritional literacy (25). Aytop and colleagues found that older adults prefer locally produced products because they find them more affordable and because of the confidence that they are produced in the country (19). Remillard et al. reported that cognitive and visual limitations that increase with age negatively affect food safety-related behaviors by limiting the ability to read and interpret food labels (26). Moreover, another study has shown that individuals perceive packaged foods as unhealthy and therefore tend to prefer fresher, unpackaged products (27). Consistent with these findings, the current study found that the majority of participants paid attention to the expiration date, but were less likely to adopt more knowledge-based behaviors such as reading labels and choosing sustainable packaging. This suggests that older adults have a basic level of food safety awareness, but lack the skills to make informed decisions.

In line with the community-based approach, “food label literacy” seminars supported by simplified, visually supported educational materials can be organized to develop informed food choices in older adults. In addition, age-appropriate information brochures and guides can be prepared in cooperation with public institutions, municipalities and Family Health Centers on issues such as the use of sustainable packaging and preference for local products to support individuals to make information-based choices.

Attitude Towards Food Waste Sub-Theme

Reducing food waste plays a critical role not only at the individual level but also in ensuring environmental and social sustainability (28). The study by Przezbórska and Wiza concluded that food waste is lower among older adults, which may be associated with long-standing habits of frugality (18). Bruce et al. found that older adults tend to evaluate leftover food and practice better portion control (29). In another study, he emphasized that behaviors to prevent food waste are often driven by habits and social norms, not by lack of knowledge, attitudes and motivation, so interventions should take these dynamics into account (30). The majority of participants exhibit conscious behaviors to prevent food waste. Strategies such as preparing portions to be consumed, storing or transforming leftovers can be considered as an important achievement in terms of sustainable nutrition. The findings suggest that older adults' attitudes and behaviors toward reducing food waste may not be solely rooted in past frugality habits, but could also be influenced by current economic constraints. This indicates that economic deprivation might be associated with more conscious food waste reduction behaviors. This finding can be interpreted as a combination of the saving habits of older adults from the past and the solution strategies they have developed under increasing economic pressures today. Reducing food waste is important in terms of both environmental sustainability and economic sustainability, and the sensitivity of older adults on this issue should be supported in community-based initiatives.

To this end, community-based approaches could include workshops on sustainable kitchen management for the older adults, hands-on trainings where local recipes are transformed and presented, or neighborhood-based “food waste reduction” campaigns. In addition, community-based food sharing networks can encourage the sharing of surplus food with neighbors or local support systems, increasing social interaction and reducing waste.

Food Shopping Attitude Sub-Theme

Food shopping is a process that directly affects the nutritional quality of individuals, and economic constraints can make this process more complex, especially for older adults (31). Chang and Hickman concluded in their study that low-income older adults are forced to limit their food expenditures, which may lead to a decline in diet quality (32). Pourebrahim and colleagues have shown that in the

face of food insecurity, older adults limit their shopping to staple and inexpensive foods, thereby reducing dietary diversity (33). Leung et al. reported that especially among older adults living in urban poverty conditions, planned shopping behaviors are driven by economic necessity, and they tend to tend towards discounted products (34). It has been determined that most participants prepare shopping lists and make planned shopping. However, these plans are shaped by restrictions such as not being able to buy some products due to lack of income or preferring only discounted products. This shows that not only physical but also economic accessibility is a problem in food access.

Accordingly, within the scope of a community-based approach, “smart shopping guidance” seminars can be organized for older adults to teach them how to shop economically and nutritiously; food voucher programs can be implemented in cooperation with social service units or discounted grocery cards for older adults on fixed incomes. In addition, technology-supported user-friendly systems can be developed to increase older adults access to digital grocery applications and facilitate price comparisons, strengthening both nutritional quality and economic management.

Nutrition Expectations Subtheme

The nutritional expectations of older adults are based not only on taste preferences but also on the need to maintain an adequate and balanced diet (35). Stoodley et al. stated that inadequate protein intake in older adults increases the risk of sarcopenia and loss of physical function and emphasized that meeting protein requirements is critical for health, especially in this period (36). Jimenez and colleagues reported that economic constraints limit access not only to meat products but also to basic food groups such as protein, fruits, dairy products and whole grains in general (37). Another study found that protein, fiber, vitamin and mineral intakes in the older adults population are below recommended levels and that one of the main reasons for this is economic inaccessibility (38). Similarly, in this study, it was observed that participants were not only interested in consuming more meat, but also in having easy access to a variety of foods (dairy products, fruits, legumes, quality cereals, etc.). Increasing pensions, lowering food prices and expanding food aid for those in need are among the most frequently expressed expectations by participants. This shows that older persons face serious socioeconomic barriers in accessing the right to adequate and balanced nutrition.

In this context, there is a need for holistic and sustainable intervention programs that support older persons' access to food within a community-based approach. Supportive models such as social market practices that include affordable and nutritious staple food groups, subsidized food packages and collective meal services are important tools to secure the right to adequate and balanced nutrition for older persons (39). However, economic and

social strategies need to be implemented simultaneously, such as increasing pensions to a level that can cover the basic living expenses of older persons, developing price policies that facilitate access to food, implementing special discounts for the older adults and ensuring equal opportunities in access to quality food. For such interventions to be implemented effectively, it is crucial that local governments, central government, civil society organizations (associations and foundations) and the private sector work in coordination. This multi-stakeholder collaboration will create a strong foundation for both resource diversity and inclusive service delivery, and will sustainably support food security for older persons (40).

This study has several limitations. Since data collection was conducted exclusively via videoconferencing, older adults with limited access to digital tools or insufficient technological literacy could not be included. This may have led to selection bias in the sample. As all data were based on self-reports, measurement limitations such as recall bias and social desirability effects may have occurred. Lastly, since all participants resided in central urban districts of metropolitan cities, the findings may not reflect the living conditions of older adults residing in rural areas. In future studies, it is recommended to include older adults from different geographical regions and diverse socioeconomic backgrounds. More inclusive samples that also cover individuals without digital access should be established to enhance the generalizability of findings, particularly in the areas of nutritional status and food availability. Accordingly, applied research evaluating the effectiveness of community-based intervention programs targeting these variables would provide valuable contributions to the field.

CONCLUSION

This study examined the dietary preferences, food access attitudes and expectations of older adults with a qualitative approach. The findings revealed that older adults attach importance to preparing meals at home, consuming fruits and vegetables and planned shopping; however, economic inadequacies limit their intake of meat and similar protein sources. While positive behaviors such as paying attention to expiry dates in food selection are common, knowledge-based habits such as reading labels and choosing sustainable packaging are less adopted. Participants exhibited conscious attitudes towards preventing food waste, utilizing leftover food and trying to minimize waste. However, economic difficulties due to the high cost of food and lack of purchasing power emerged as a common problem in food shopping. In terms of nutritional expectations, the desire to consume more animal products, the desire to increase pensions, and the desire to have access to affordable foods stand out. These findings show that the nutritional behaviors of older adults are shaped by both economic and knowledge levels, and emphasize the importance of trainings, social support programs and sustainable community-based interventions to increase nutritional literacy.

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The Self-Efficacy of Nursing Students in Medication Administration to Children

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Abstract

Aim: This study aimed to determine the level of self-efficacy of nursing students in administering medications to children and to identify demographic, educational, and clinical factors associated with self-efficacy.

Material and Method: This study was a descriptive cross-sectional study. The sample included 260 nursing students from a Turkish university. Data were collected between 10 April 2025 and 21 April 2025. Convenience sampling methods was used to recruit participants. Data were collected using a questionnaire comprising socio-demographic questions and the Medication Administration Self-Efficacy Scale in Children for Nursing Students. The data were analysed using SPSS 22.0.

Results: The mean self-efficacy score was 43.63 ± 14.15 , indicating a moderate level. Higher self-efficacy was observed in male students, upperclassmen (3rd and 4th year), and those with prior experience or education in paediatric medication administration. Statistically significant associations were found between higher self-efficacy and receiving relevant education, finding that education sufficient, having prior hands-on experience, feeling confident during medication administration, and having adequate dosage calculation knowledge ($p < 0.05$). The most commonly reported challenges faced while treating children included anxious parents (55.4%), fear of failure (37.3%), the child's non-compliance with treatment (33.5%), and lack of dosage knowledge (23.5%).

Conclusion: Nursing students' self-efficacy in paediatric medication administration was moderate and was influenced by experience, education, and confidence. Addressing low self-efficacy is crucial to minimize potential errors and anxiety in paediatric medication administration. It is recommended to enhance practical training and establish supportive educational environments to improve students' self-efficacy.

Keywords: Self-efficacy, medication administration, children, paediatric, nursing students

INTRODUCTION

Self-efficacy, defined as one's belief in their capabilities to execute behaviours necessary to produce specific performance attainments, serves as a critical determinant in achieving success in clinical nursing settings (1). High levels of self-efficacy have been associated with improved learning outcomes and task performance among nursing students (2,3). In the domain of medication administration, self-efficacy influences students' preparedness, confidence, and accuracy in delivering safe and effective care to children (3,4). It is important for nursing students to possess self-efficacy in medication administration to children for correct medication administration (5). Research indicates that various factors, including practical experience and

pedagogical methods, significantly impact self-efficacy levels among nursing students (2,6). Programs integrating simulation and hands-on training enhance self-efficacy by providing students with realistic exposure to clinical scenarios, thereby improving their competence in medication administration (6). Additionally, supportive educational environments play a vital role in fostering self-efficacy by offering encouragement and constructive feedback (7,8).

Implementing targeted interventions designed to improve self-efficacy can lead to improved academic outcomes and lower anxiety levels among nursing students, especially when dealing with high-pressure tasks (9,10). Frequently, nursing students expressing concerns about administering medication express a perceived lack of preparation,

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highlighting the necessity for curricula that promote confidence-building (3,4). Administering medication to children poses some challenges due to physiological differences and potential adverse reactions; therefore, nursing students require both relevant knowledge and the necessary confidence to apply that knowledge effectively (6,11). Understanding the self-efficacy of nursing students is essential for developing educational strategies that promote greater competence and safety in paediatric nursing care. Exploring nursing students' self-efficacy in medication administration to children is critical for enhancing educational outcomes and ensuring patient safety. Given the high prevalence of medication errors in paediatric settings, often attributed to factors such as inadequate knowledge and calculation skills, improving self-efficacy of nursing students is essential to prepare future nurses for the complexities associated with paediatric medication administration. This study aimed to determine the level of self-efficacy of nursing students in administering medications to children and to identify demographic, educational, and clinical factors associated with self-efficacy.

MATERIAL AND METHOD

Study Design

This study is a descriptive cross-sectional study.

Settings, Participants, and Sampling

The setting of this study was the Faculty of Health Sciences at a Public University located in the southeast of Turkey. The population of the study consists of nursing students in their 2nd, 3rd, and 4th years of study (n=297). These cohorts were selected to represent varying levels of clinical experience and theoretical instruction, particularly regarding paediatric medication administration. While not all students had received the same level of training in paediatric medication administration, this variation allowed us to assess how factors such as prior education and hands-on experience affect self-efficacy levels.

Inclusion criteria were: being an actively enrolled nursing student in the 2nd, 3rd, or 4th year of study and voluntarily agreeing to participate in the study. No exclusion criteria were applied regarding previous healthcare work experience (e.g., nurse aide roles), as prior experience was one of the variables examined in relation to self-efficacy. A total of 260 nursing students participated in the study. Convenience sampling methods was used to recruit participants.

Data Collection

Data were collected between 10 April 2025 and 21 April 2025. The data were collected by using questionnaire technique with a data collection form consisting of 2 parts. The researchers explained the aim of the study to the participants. After participants were informed that their participation was voluntary and that they could leave without reason, the questionnaire was distributed as hard copies to the nursing students to be filled out during their free time. The questionnaires were filled out by the nursing students and were collected by the researchers. The time to fill out the questionnaire took about 10 minutes.

Data collections forms

Socio-demographic information form:

It consists of a total of 18 questions related to the sociodemographic characteristics of the nursing students and their experiences regarding medication administration in children including their gender, classes, internship workplace, status of receiving education on child health, status of finding the received education sufficient, status of performing interventions on children before, status of administering medication to children before, a reluctance to apply treatment to children, self-confidence when administering medication to children, the adequacy of dosage calculation knowledge in paediatric patients, status of administering medication to paediatric patients in the correct way, ability to explain medication application processes, knowing how to approach the situation when paediatric patients refuse to take medication, knowing techniques to calm the paediatric patients during medication administration, knowing how to act after wrong practices on paediatric patients, and information of medication error prevention.

Medication Administration Self-Efficacy Scale in Children for Nursing Students:

This scale was developed by Bektaş et al. (12). The scale consists of 16 items and 2 sub-dimensions. In the reliability analysis conducted regarding the internal consistency of the Medication Administration Self-Efficacy Scale in Children for Nursing Students, the Cronbach's Alpha coefficient obtained for the entire scale was calculated as .94. This value indicates that the scale has a very high internal consistency. When looking at the sub-dimensions of the scale; the Cronbach's Alpha coefficient for the "medication preparation self-efficacy" sub-dimension was found to be .91, while it was .87 for the "medication application self-efficacy" sub-dimension.

Data Analysis

The data were analysed using the SPSS 22.0 statistical program. Frequency and percentage analyses were used to determine the descriptive characteristics of the participants in the study, while mean and standard deviation statistics were utilized in examining the scale. Kurtosis and Skewness values were examined to determine whether the research variables exhibited normal distribution. In the relevant literature, it is accepted that the results of the kurtosis and skewness values of the variables fall between +1.5 and -1.5 (13), and between +2.0 and -2.0 (14) to be considered normally distributed. It has been determined that the variables exhibit a normal distribution. Parametric methods were used in the analysis of the data. In examining the differences in scale levels according to the descriptive characteristics of the participants, independent samples t-test, one-way analysis of variance (ANOVA), and post hoc analyses (Tukey, LSD) were utilized.

Ethical Consideration

Ethical approval was obtained from the Mardin Artuklu University Non-Invasive Clinical Research Ethics Committee

(Date: 25/03/2025; Reference number: 2025/3-2). Institutional permission was granted from the Mardin Artuklu University, Faculty of Health Sciences (Date: 09/04/2025; Reference number: E-53920853-101.04-191420). Informed consent was obtained from all participants. The study was carried out in accordance with the principles of the Declaration of Helsinki.

RESULTS

Descriptive characteristics of the participants were provided

in Table 1. Of participants, 65.4% were female, 30% were in the second class, 32.3% were in the third class, and 37.7% were in the fourth class. 33.5% of the students were practicing in the paediatric emergency department, while 66.5% were practicing in the paediatric ward. 61.9% of the participants indicated that they received training on medication application for paediatric patients, while the percentage of those who considered this training sufficient remained at 33.5%. The mean age of the participants was 22.53±2.98, with ages ranging from 19 to 39.

Table 1. Descriptive characteristics of the participants		
Variables	n	%
Gender		
Male	90	34.6
Female	170	65.4
Class		
2	78	30.0
3	84	32.3
4	98	37.7
Internship workplace		
Paediatric emergency department	87	33.5
Paediatric clinics	173	66.5
Status of receiving education on child health		
Yes	161	61.9
No	99	38.1
Status of finding the received education sufficient		
Yes	87	33.5
No	173	66.5
	Mean	SD
Age	22.530	2.977
SD: standard deviation		

Nursing student experiences regarding medication administration in children were provided in Table 2. The proportion of those who performing interventions on children before was 53.1%, while the proportion of those who reported administering medication was 56.9%. Of students, 66.9% expressed that they hesitated to perform procedures on children, while 51.2% stated that they felt confident when administering medication to children.

The most commonly reported challenges faced while treating children include excessively anxious and interventionist parents (55.4%), anxiety and fear of failure (37.3%), the child's non-compliance with treatment (33.5%), lack of knowledge about paediatric dosage and equipment (23.5%), time pressure (21.5%), inability to find age-appropriate language (21.2%), and traumatic experiences (4.6%).

When the evaluations of participants regarding dosage calculation knowledge in children were examined, 21.5% considered themselves sufficient, 26.9% insufficient, and 51.5% moderately sufficient. The proportion of those who stated they have corrected knowledge of the medication

route was 43.8%, while 16.2% indicated they do not have this knowledge, and 40.0% expressed that they have partial knowledge. The proportion of those who stated they have the ability to explain the process was 36.5%, while 15.8% see this ability as insufficient, and 47.7% find it moderately sufficient.

30% of the participants expressed that they consider themselves sufficient in developing an approach in the situation when paediatric patients refuse to take medication, while 23.1% feel insufficient, and 46.9% stated that they were partially sufficient. The proportion of those who claimed to have knowledge of calming techniques was 31.5%, while 20.8% stated they do not have knowledge about this, and 47.7% said they have partial knowledge regarding such calming techniques. The percentage of those who know how to act after a wrong application was 25.4%, those who stated they do not know how to act was 30.4%, and the those who partially know was 44.2%. Lastly, 34.6% expressed that they have knowledge to prevent medication errors, 25% stated they feel insufficient in this regard, and 40.4% claimed to have partial knowledge in this regard.

Table 2. Nursing student experiences regarding medication administration in children		
Variables	n	%
Status of performing interventions on children before		
Yes	138	53.1
No	122	46.9
Status of administering medication to children before		
Yes	148	56.9
No	112	43.1
Hesitancy to apply treatment to children		
Yes	174	66.9
No	86	33.1
Self-confidence when administering medication to children		
Yes	133	51.2
No	127	48.8
Challenges encountered while treating child patients*		
Excessively anxious and interventionist parents	144	55.4
Child's noncompliance with treatment	87	33.5
Lack of knowledge about paediatric dosage and equipment	61	23.5
Time pressure	56	21.5
Anxiety and fear of failure	97	37.3
Inability to find age-appropriate language	55	21.2
Traumatic experiences	12	4.6
The adequacy of dosage calculation knowledge in paediatric patients		
Yes	56	21.5
No	70	26.9
Partly	134	51.5
Status of administering medication to paediatric patients in the correct way		
Yes	114	43.8
No	42	16.2
Partly	104	40.0
Ability to explain medication application processes		
Yes	95	36.5
No	41	15.8
Partly	124	47.7
Knowing how to approach the situation when paediatric patients refuse to take medication		
Yes	78	30.0
No	60	23.1
Partly	122	46.9
Knowing techniques to calm the paediatric patients during medication administration		
Yes	82	31.5
No	54	20.8
Partly	124	47.7
Knowing how to act after wrong practices on paediatric patients		
Yes	66	25.4
No	79	30.4
Partly	115	44.2
Information of medication error prevention		
Yes	90	34.6
No	65	25.0
Partly	105	40.4
*More than one option could be selected		

The total and sub-dimension mean scores of nursing students regarding the “Medication Administration Self-Efficacy Scale in Children for Nursing Students” have been examined in Table 3. The overall mean score obtained from the scale was 43.63 ± 14.15 , varying between a minimum of 16 and a maximum of 74 scores. This result indicates that the students' self-efficacy levels regarding medication applications in children were at a moderate level. In the sub-dimension of “medication preparation self-efficacy”, the mean score has been determined as 20.79 ± 7.30 ; the

scores of students in this sub-dimension were distributed between 8 and 38. In the other sub-dimension, “medication administration self-efficacy,” the mean score was 22.84 ± 7.64 , with participants' scores ranging from 8 to 37. These mean scores for the sub-dimensions indicate that students feel less proficient in the medication preparation processes compared to their medication administration skills. These results emphasize the need for structured educational content to support self-efficacy in paediatric medication administration within nursing education.

Table 3. Mean self-efficacy scores for medication administration in children								
	N	Mean	SD	Min.	Max.	Scale range	Kurtosis	Skewness
Medication Administration Self-Efficacy Scale in Children for Nursing Students	260	43.631	14.152	16.000	74.000	16-80	-0.789	-0.134
Medication preparation self-efficacy	260	20.789	7.302	8.000	38.000	8-40	-0.715	0.075
Medication application self-efficacy	260	22.842	7.644	8.000	37.000	8-40	-0.869	-0.205

Table 4 examines whether the self-efficacy scores of nursing students related to medication applications in children differ according to various descriptive characteristics. In the analyses conducted by gender, although the mean self-efficacy scores of male students were higher than those of female students, this difference was not found to be statistically significant in the overall total ($p=0.124$). However, a significant difference in favour of male students was found in the sub-dimension of “medication preparation self-efficacy” ($p=0.021$). In the analyses performed according to class level, significant differences were found in terms of all sub-dimensions and total scores ($p<0.001$). Third-class and fourth-class students have higher self-efficacy scores compared to second class students. However, although the scores of students working in the paediatric emergency department were higher than those working in the paediatric unit, this difference was not found to be statistically significant ($p>0.05$).

Students who received training on medication administration for children have significantly higher self-efficacy scores compared to those who did not receive such training ($p=0.000$). Similarly, this study found that students who find the training sufficient have higher total and subdimension scores compared to those who do not find it sufficient ($p<0.05$).

Students who have previously administered interventions

and medications to children reported significantly higher self-efficacy scores compared to those without experience ($p<0.01$). Students who stated they do not hesitate to practice have higher scores than those who were hesitant ($p<0.05$). Students who expressed confidence in themselves also had significantly higher scores ($p=0.000$).

Students who have knowledge about dosage calculation have scored significantly higher than those who do not; the mean score for those who answered 'yes' was 51.05, while for those who answered 'no' it was determined to be 34.61 ($p=0.000$). In all variables such as having correct knowledge about the right route, ability to explain the process, knowing the appropriate approach in case the child refuses the medication, knowing of calming techniques, knowing the correct behaviour after a wrong application, and being knowledgeable about preventing medication errors, it was found that students who had knowledge scored significantly higher ($p<0.01$).

In general, it was observed that students with higher levels of experience, education, and knowledge have higher scores both in the total self-efficacy score and in the sub-dimensions of “medication preparation self-efficacy” and “medication application self-efficacy”. These results emphasize the importance of both theoretical and practical education to enhance self-efficacy in medication administration among children.

Table 4. The differentiation of self-efficacy scores of medication applications in children according to descriptive characteristics				
Variables	n	Medication Administration Self-Efficacy Scale in Children for Nursing Students	Medication preparation self-efficacy	Medication application self-efficacy
		Mean±SD	Mean±SD	Mean±SD
Gender				
Male	90	45.49±14.32	22.22±7.29	23.27±7.58
Female	170	42.65±14.01	20.03±7.22	22.62±7.69
t		1.545	2.323	0.651
p		0.124	0.021	0.516

F: Anova Test; t: Independent Groups T-Test; PostHoc: Tukey, LSD

Table 4. The differentiation of self-efficacy scores of medication applications in children according to descriptive characteristics				
Variables	n	Medication Administration Self-Efficacy Scale in Children for Nursing Students	Medication preparation self-efficacy	Medication application self-efficacy
		Mean±SD	Mean±SD	Mean±SD
Class				
2	78	37.05±13.57	17.35±6.60	19.71±7.67
3	84	46.76±14.62	22.49±7.89	24.27±7.44
4	98	46.18±12.48	22.07±6.39	24.11±7.11
F		13.220	13.673	10.050
p		0.000	0.000	0.000
PostHoc		2>1, 3>1 (p<0.05)	2>1, 3>1 (p<0.05)	2>1, 3>1 (p<0.05)
Internship workplace				
Paediatric emergency department	87	45.09±15.18	21.38±7.95	23.71±8.08
Paediatric clinics	173	42.90±13.59	20.49±6.96	22.40±7.40
t		1.182	0.925	1.304
p		0.238	0.356	0.194
Status of receiving education on child health				
Yes	161	46.57±13.90	22.22±7.13	24.35±7.58
No	99	38.85±13.28	18.45±7.01	20.39±7.13
t		4.423	4.167	4.176
p		0.000	0.000	0.000
Status of finding the received education sufficient				
Yes	87	47.11±14.62	22.72±7.63	24.39±7.77
No	173	41.88±13.62	19.82±6.95	22.06±7.48
t		2.854	3.080	2.336
p		0.005	0.002	0.020
Status of performing interventions on children before				
Yes	138	46.62±14.83	22.41±7.70	24.22±7.77
No	122	40.25±12.57	18.96±6.38	21.29±7.22
t		3.715	3.901	3.137
p		0.000	0.000	0.002
Status of administering medication to children before				
Yes	148	45.96±14.28	21.93±7.22	24.03±7.76
No	112	40.55±13.43	19.28±7.17	21.28±7.24
t		3.100	2.946	2.914
p		0.002	0.004	0.004
Hesitancy to apply treatment to children				
Yes	174	41.94±13.63	19.80±7.00	22.14±7.48
No	86	47.05±14.64	22.78±7.53	24.27±7.81
t		-2.771	-3.143	-2.128
p		0.006	0.002	0.034
Self-confidence when administering medication to children				
Yes	133	47.92±14.45	23.18±7.43	24.74±7.64
No	127	39.14±12.38	18.28±6.28	20.86±7.16
t		5.248	5.727	4.220
p		0.000	0.000	0.000
The adequacy of dosage calculation knowledge in paediatric patients				
Yes	56	51.05±15.86	25.04±7.83	26.02±8.55
No	70	34.61±11.73	16.13±5.81	18.49±6.69
Partly	134	45.24±12.08	21.45±6.44	23.79±6.72
F		27.422	29.637	19.724
p		0.000	0.000	0.000
PostHoc		1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2 (p<0.05)

F: Anova Test; t: Independent Groups T-Test; PostHoc: Tukey, LSD

Table 4. The differentiation of self-efficacy scores of medication applications in children according to descriptive characteristics

Variables	n	Medication Administration Self-Efficacy Scale in Children for Nursing Students	Medication preparation self-efficacy	Medication application self-efficacy
		Mean±SD	Mean±SD	Mean±SD
Status of administering medication to paediatric patients in the correct way				
Yes	114	47.75±15.49	22.89±7.92	24.86±8.10
No	42	36.83±13.36	17.64±6.95	19.19±7.17
Partly	104	41.86±11.33	19.75±6.01	22.11±6.63
F		11.341	10.393	9.879
p		0.000	0.000	0.000
PostHoc		1>2, 3>2, 1>3 (p<0.05)	1>2, 1>3 (p<0.05)	1>2, 3>2, 1>3 (p<0.05)
Ability to explain medication application processes				
Yes	95	47.60±15.28	23.20±8.00	24.40±7.91
No	41	34.95±11.07	16.34±5.51	18.61±6.55
Partly	124	43.46±12.89	20.41±6.50	23.05±7.31
F		12.471	14.275	8.802
p		0.000	0.000	0.000
PostHoc		1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2 (p<0.05)
Knowing how to approach the situation when paediatric patients refuse to take medication				
Yes	78	46.96±15.26	22.35±7.96	24.62±7.98
No	60	36.83±12.86	18.08±6.95	18.75±6.53
Partly	122	44.84±12.97	21.12±6.71	23.72±7.26
F		10.207	6.264	12.526
p		0.000	0.002	0.000
PostHoc		1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)
Knowing techniques to calm the paediatric patients during medication administration				
Yes	82	46.09±16.13	22.04±8.33	24.05±8.48
No	54	37.28±13.44	18.09±6.98	19.19±7.16
Partly	124	44.77±12.23	21.14±6.42	23.64±6.79
F		7.431	5.181	8.316
p		0.001	0.006	0.000
PostHoc		1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)
Knowing how to act after wrong practices on paediatric patients				
Yes	66	48.33±15.51	23.35±7.84	24.98±8.25
No	79	37.37±14.11	17.59±7.08	19.77±7.70
Partly	115	45.23±11.80	21.51±6.36	23.72±6.59
F		13.268	13.336	10.433
p		0.000	0.000	0.000
PostHoc		1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)	1>2, 3>2 (p<0.05)
Information of medication error prevention				
Yes	90	48.57±14.79	23.63±7.53	24.93±7.95
No	65	37.28±12.81	17.54±6.85	19.74±7.01
Partly	105	43.33±12.82	20.36±6.45	22.97±7.17
F		13.182	14.888	9.300
p		0.000	0.000	0.000
PostHoc		1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2, 1>3 (p<0.05)	1>2, 3>2 (p<0.05)

F: Anova Test; t: Independent Groups T-Test; PostHoc: Tukey, LSD

DISCUSSION

This study found that the overall self-efficacy scores of the nursing students were at a moderate level. Similarly, a study conducted by Akça and Berşe (2023) determined that the self-efficacy levels of nursing students in medication administration to children were also at a moderate level,

and that self-efficacy was negatively related to clinical decision-making skills. This situation indicates that students may behave more cautiously or hesitantly in their decision-making processes when they do not feel competent. This result reveals that the level of self-efficacy has a direct impact on clinical safety (5).

When the sub-dimensions of the scale were examined, it was observed that students feel less competent in the medication preparation processes. Şahin et al. (2023) have shown that structured educational models such as nurse mentoring and peer mentoring are effective in increasing students' self-efficacy levels during the clinical practice process. Especially direct clinical support and guidance for medication applications have enabled students to gain more confidence in both preparation and application processes (15). Similarly, a study conducted by Dinç et al. (2024) found that the concept map-based education significantly increased students' self-efficacy levels regarding medication administration in children. This indicates that the structuring of theoretical knowledge at a conceptual level and its systematic presentation can effectively reflect in clinical practice (16).

Additionally, a study conducted by Gezer and Alemdar (2024) found that paediatric nursing competency plays a partial mediating role in the relationship between medication administration self-efficacy and the tendency for medical errors in children (17). These results suggest that higher self-efficacy and nursing competence may be associated with a lower tendency to make medication errors (17).

This study found that individual and environmental factors such as qualifications, educational level, practical experience, and cognitive competencies significantly affect the self-efficacy levels of nursing students regarding medication administration in children. In line with results of this study, a study conducted by Akça and Berşe (2023) found that male students and those in their fourth year had higher self-efficacy levels. Moreover, students who do not experience anxiety had significantly higher self-efficacy levels (5). Similarly, Gezer and Alemdar (2024) demonstrated that self-efficacy is influenced not only by individual competencies but also by broader professional competencies such as paediatric nursing competence, and that this variable is associated with the tendency for medical errors (17).

In addition, education factor also emerges as an important factor in self-efficacy of nursing students. Importantly, this showed that training exposure was not equally distributed across academic years, with most 2nd-year students lacking structured paediatric training. This disparity may partially explain the lower self-efficacy scores observed in this group. Subgroup analyses confirmed that self-efficacy was higher among trained students within each year, suggesting that both academic seniority and training exposure independently contribute to self-efficacy. Educational strategies such as structured mentoring and concept map-based instruction have been shown to enhance nursing students' self-efficacy. For example, Şahin et al. (2023) demonstrated that both nurse mentoring and peer mentoring significantly improved students' self-efficacy and reduced clinical anxiety (15). Similarly, concept map-based education was found to strengthen students'

theoretical foundations and boost confidence in paediatric medication administration (18). Moreover, the direct relationship between knowledge level and self-efficacy is also emphasized. Jones et al. (2022) indicated that a high level of self-efficacy is seen together with the recognition of medication errors, and knowledgeable and conscious students have higher levels of self-efficacy (3). These results suggest that multifaceted, supportive educational interventions can positively impact self-efficacy.

An important consideration in interpreting the results is the variability in paediatric educational exposure across academic years. In our sample, structured training in paediatric medication administration was more prevalent among 3rd- and 4th-year students, as this content is typically introduced during the latter part of the nursing curriculum. This disparity in training likely contributed to the lower self-efficacy scores observed in 2nd-year students. Therefore, differences in self-efficacy across academic years may reflect not only clinical maturity but also unequal access to formal paediatric education. Future research and curriculum planning should account for this timing to ensure earlier and more equitable exposure to paediatric medication competencies.

Implications and Recommendations

In light of the results from this study, several implications and recommendations can be drawn to enhance nursing education and practice, particularly concerning the self-efficacy of nursing students in medication administration to children. Self-efficacy is pivotal for achieving success in nursing, especially in high-stakes situations such as medication administration to paediatric patients. Therefore, it is essential to cultivate self-efficacy among nursing students through targeted educational strategies. Educational programs should incorporate practical training sessions that simulate real clinical environments, enabling students to practice skills in a safe and controlled setting.

Moreover, identifying demographic, educational, and clinical factors that correlate with self-efficacy levels can inform curricular design. Educators should consider these factors to tailor training programs to meet the diverse needs of their students. To maximize the self-efficacy of nursing students, educational institutions should adopt comprehensive training programs tailored to individual and group needs, facilitate practical experiences, and promote an environment of collaboration and mutual support. These strategies could ensure that future nurses are well-equipped to deliver safe and effective care to paediatric patients, ultimately contributing to improved patient outcomes.

Strengths and Limitations

This study provides valuable insights into the self-efficacy of nursing students in paediatric medication administration, a critical yet understudied area in nursing education. The use of a validated scale (Medication Administration Self-Efficacy Scale in Children for Nursing Students)

with high reliability (Cronbach's $\alpha=0.94$) strengthens the methodological rigor of the results. The inclusion of a relatively large sample size ($n=260$) and the examination of diverse factors, such as demographic characteristics, educational background, and clinical experience, enhance the comprehensiveness of the study. Additionally, the focus on both preparation and application sub-dimensions of self-efficacy offers a nuanced understanding of students' confidence levels.

Despite these strengths, the study is not without limitations. One of the limitations was the reliance on self-reported measures of self-efficacy, which may introduce response biases. Participants might overestimate or underestimate their confidence levels due to social desirability or subjective perceptions of their abilities. This can affect the accuracy and reliability of the results. Additionally, this study was conducted in only one university, therefore, the results may not be generalizable to all PEDs. However, the results of this study concurred with the existing literature.

CONCLUSION

This study found that the students' self-efficacy levels regarding medication applications in children were at a moderate level. This study revealed that students with higher levels of experience, education, and knowledge have higher scores both in the total self-efficacy score and in the sub-dimensions of "medication preparation self-efficacy" and "medication application self-efficacy". The investigation into the self-efficacy of nursing students in medication administration to children reveals significant implications for both nursing education and clinical practice. This study demonstrate that higher levels of self-efficacy are closely associated with improved learning outcomes, which is essential considering the complexities and responsibilities involved in paediatric medication administration.

Furthermore, by identifying key demographic, educational, and clinical factors that contribute to variations in self-efficacy levels among nursing students, this research provides a foundation for targeted interventions in nursing curricula. This study emphasised the importance of developing support mechanisms and training programs that can enhance students' confidence and competency in clinical practices. As nursing education continues to evolve, it is imperative for educators to incorporate strategies that improve self-efficacy, thereby ensuring that future nurses are well-prepared to provide safe and effective care for paediatric populations. The insights gained from this study not only contribute to academic discourse but also serve as a call to action for nursing institutions to prioritize the development of self-efficacy through comprehensive educational practices. Ultimately, by fostering self-efficacy, nursing programs can better equip graduates to navigate the challenges of healthcare delivery, especially in high-stakes environments where the administration of medications to children is concerned.

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Nd:YAG Laser Application Enhances Wound Healing After Gingivectomy: A Histopathological Evaluation

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Abstract

Aim: Nd:YAG laser therapy is known for its stimulatory and wound-healing acceleration effects and antimicrobial efficacy by eliminating periodontal pathogens and stimulating fibroblasts. This study aims to histopathologically evaluate the impact of Nd:YAG laser treatment applied after gingivectomy/plasty on wound healing in patients with chronic inflammatory gingival hyperplasia.

Material and Method: This study included 25 systemically healthy individuals with chronic inflammatory gingival hyperplasia. The areas receiving Nd:YAG laser and gingivectomy/plasty were randomly assigned to the test group. In contrast, regions receiving only gingivectomy/plasty were assigned to the control group. Clinical periodontal measurements, including Plaque Index (PI), Gingival Index (GI), Bleeding on Probing (BOP), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL), were obtained before and after initial periodontal therapy (IPT) and after gingivectomy/plasty. Superficial Cell Index (SCI) and Keratinization Index (KI) were determined through histopathological examination of gingival tissue samples obtained by exfoliative cytology before and after Nd:YAG laser treatment.

Results: Significant reductions were observed in clinical periodontal measurements (PI, GI, BOP, PPD) after IPT compared to baseline values ($P<0.05$). A decrease was also noted in clinical periodontal measurements after gingivectomy/plasty ($P<0.05$). When SCIs and KIs were assessed, a decrease was observed on the first day post-gingivectomy/plasty, followed by an increase in both groups, with a more pronounced increase in the Nd:YAG laser group ($P<0.05$).

Conclusion: Similar to the association between IPT and periodontal measurements, Nd:YAG laser treatment following gingivectomy/plasty significantly affected the gingival tissue SCI and KI, positively influencing clinical periodontal healing over time.

Keywords: Gingival hyperplasia, Nd:YAG laser, superficial cell index, keratinization index, gingivectomy

INTRODUCTION

Gingival hyperplasia is a common periodontal condition that alters gingival morphology and histology (1). It is clinically characterized by gingival hyperplasia, color changes, and bleeding on probing. The primary cause of hyperplasia is the increase in intercellular fibers and cellular elements (2). This condition develops due to the interaction between the host and bacterial plaque, leading to a host response, and is defined as a prevalent gingival pathology. Its etiology includes factors, such as medication use, systemic diseases, pregnancy, vitamin C deficiency, hormonal changes during puberty, and genetic disorders (2,3). Factors like dental crowding, cervical cavities, non-functional teeth, fixed prostheses, mouth breathing, food impaction, and orthodontic appliances can contribute to chronic inflammatory gingival hyperplasia (4).

Gingivectomy/plasty and periodontal flap procedures are used in periodontology to correct gingival morphology and

restore natural gingival anatomy. These treatments can be performed using conventional, electrosurgery, or laser surgery (5). Factors influencing post-gingivectomy wound healing; wound care during this period is critical. Despite patient diligence, some post-surgical complications are inevitable. Various chemical agents and herbal preparations have been used to minimize the complications, but their efficacy remains controversial and may cause undesirable side effects (2). Recent studies demonstrated that low-dose laser accelerates wound healing through biostimulation, enhancing patient comfort post-surgery (1,3,6).

The wound-healing process depends on the type of laser used, the wavelength and frequency of the light, and the laser's mechanism of action (7). Each type of laser applied to soft tissue has different absorption and penetration degrees. Generally, primary closure wounds heal more slowly after laser surgery than conventional surgery. However, studies have shown that laser application after

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conventional surgery accelerates wound healing, with low-dose laser therapy positively affecting the biostimulation of organisms (3,5,7). This study aims to histopathologically examine the effects of Nd:YAG laser application on wound healing following gingivectomy/ gingivoplasty in individuals with chronic inflammatory gingival hyperplasia.

MATERIAL AND METHOD

Ethical Statement

The study was conducted at a university hospital and adhered strictly to the ethical guidelines of the Declaration of Helsinki. The study was approved by the Ethics Committee of Atatürk University Faculty of Dentistry (Meeting Date: 25.10.2017, Meeting No: 13/2017, Decision No: 82), and conducted in accordance with the provisions of the Regulation on Clinical Trials issued by the Ministry of Health of the Republic of Türkiye.

Study Design

This study was designed as a prospective, randomized, controlled trial to evaluate the impact of Nd:YAG laser application on wound healing following gingivectomy in patients with chronic inflammatory gingival hyperplasia. A total of 25 systemically healthy patients (13 males, 12 females) aged 15–40 years were enrolled. A detailed schematic flowchart of the study protocol has been added to illustrate the sequence of interventions and evaluations (Figure 1: flowchart). Inclusion criteria consisted of clinically diagnosed chronic inflammatory gingival hyperplasia involving at least six affected teeth, good general health with no systemic conditions that could affect wound healing, and a willingness to comply with study requirements. Patients with active periodontal disease, smoking habits, or a history of laser therapy in the past six months were excluded from participation. Only anterior regions were included to standardize the surgical field and healing dynamics. A split-mouth design was used, with one side receiving laser treatment while the contralateral site was managed conventionally and covered with a periodontal dressing.

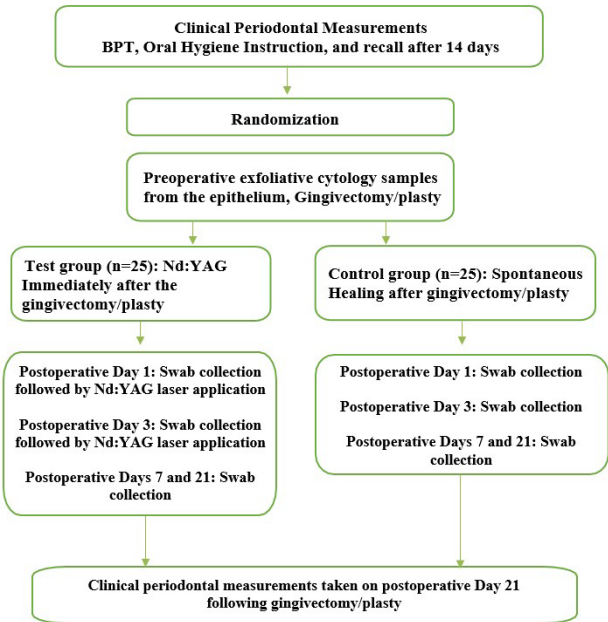


Figure 1. Flowchart of the patient Nd:YAG application

Grouping and Treatment Protocol

Participants were randomly assigned into groups: the Test Group (n=13), who underwent conventional gingivectomy followed by adjunctive Nd:YAG laser application (Figure 2), and the Control (n=12), who underwent gingivectomy alone with no laser intervention. All interventions were performed by a clinician (Onural Butay Ozturk). Randomization was achieved using a computer-generated sequence, and treatment allocation was concealed until intervention. The gingivectomy procedure was performed using a standard external bevel surgical technique under local anesthesia (2% lidocaine with 1:100,000 epinephrine). Following gingivectomy, the test group received Nd:YAG laser treatment with the following parameters: wavelength of 1064 nm, pulse duration of 100 μs, power setting of 1.5 W, and a repetition rate of 20 Hz. The laser was applied in a non-contact, sweeping motion across the surgical site for 30 seconds per affected region. The control group received only conventional gingivectomy without additional laser therapy. A single experienced clinician performed all surgical procedures to ensure technical consistency and protocol adherence throughout the study. Periodontal parameters were calibrated by a single examiner using a standardized periodontal probe at mesial, distal, midfacial, and palatal sites, at the same time of day. Patients with less than 10% Bleeding on Probing (BOP) following non-surgical initial periodontal therapy (IPT) were included.



Figure 2. A sample picture of the Nd:YAG laser

Clinical Assessments and Follow-Up

The study utilized a split-mouth design to minimize inter-individual variability. Both laser and conventional surgical techniques were performed on standardized regions, and uniform oral hygiene instructions were provided to all patients. Clinical periodontal assessments were conducted at baseline and post-treatment on the 7th and 14th days. These evaluations included the, Plaque Index (PI), which was assessed using the Silness and Løe method, and the Gingival Index (GI), which was evaluated according to Løe and Silness criteria. BOP was measured using a gentle probing technique, while Probing Pocket Depth (PPD) was determined at six sites per tooth using a Williams periodontal probe. Additionally, Clinical Attachment Level (CAL) was measured from the cemento-enamel junction to the base of the pocket. Periodontal parameters were first recorded

on Day 14 following non-surgical therapy, and again on Day 21 post-surgical intervention to capture healing outcomes. All assessments were performed by a single calibrated examiner blinded to group allocation. Analgesic use was deliberately limited postoperatively to accurately evaluate postoperative pain as a primary outcome measure. Patients were advised to use paracetamol if needed, which lacks anti-inflammatory effects that could influence healing. Patients were provided with detailed postoperative care instructions, including the use of chlorhexidine mouthwash twice daily and avoidance of mechanical trauma to the surgical site. Follow-up visits were scheduled on the 7th and 14th days to assess healing progress and record any complications. Clinical periodontal measurements were conducted by the same calibrated examiner using a 0.5 mm Williams periodontal probe (Hu-Friedy, Chicago, IL, USA).

Histopathological Analysis

Gingival tissue samples were obtained before and after treatment via biopsy. Gingival biopsies were obtained separately at baseline (before treatment) and post-treatment to evaluate histological changes. Gingival tissue biopsies were collected immediately post-surgery (Day 0), and on Days 1, 3, 7, and 21 from laser-treated and non-treated sites. Immediately after collection, the samples were fixed in 10% formalin and processed for histological examination using hematoxylin-eosin staining. Histopathological parameters were evaluated based on specific indices, including the Superficial Cell Index (SCI), which was quantified by assessing epithelial thickness and superficial cell proliferation (8). The degree of keratin layer formation was measured to determine Keratinization Index (KI) (9). Fibroblast activity was evaluated by examining fibroblast density and collagen deposition within the connective tissue. Tissue evaluation was conducted using light microscopy, and images were captured for documentation and comparative analysis. A single-blinded

histopathologist, Dr. Betül Gündoğdu. performed all histopathological assessments to ensure consistency. The SCI and KI calculations were based on established methods previously described in the literature (8,9).

Statistical Analysis

All statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA). A priori power analysis was conducted based on a reference indicating that a sample size of 21 participants would achieve 95% power. Sample size calculation was performed according to the study of Gopal et al. (7). To account for potential dropouts, 25 patients were enrolled. Descriptive statistics were used to summarize baseline characteristics. Continuous variables were assessed for normality using the Shapiro-Wilk test. Between-group comparisons were conducted using an independent t-test for normally distributed data and the Mann-Whitney U test for non-parametric variables. A repeated analysis of variance (ANOVA) was employed to evaluate changes over time within each group. A P-value of <0.05 was considered significant.

RESULTS

Demographic Characteristics

The mean age of the participants was 23.60±4.50 years, reflecting a young adult population with a balanced gender distribution. All subjects exhibited generalized gingival hyperplasia secondary to chronic inflammation, with no systemic comorbidities reported. Postoperative healing was uneventful in all cases, with no edema, erythema, suppuration, or abscess formation observed during follow-up. Full-mouth clinical periodontal parameters—PI, GI, BOP, PD, and CAL—were evaluated at three stages: baseline, after IPT and post-gingivectomy/plasty (Table 1). Periodontal parameters listed in Table 1 were recorded on postoperative day 14.

Table 1. Clinical periodontal parameters at baseline, post-IPT, and post-gingivectomy/plasty				
Parameters	Baseline	Post-IPT	Post-Surgery	P-value*
PI	2.29±0.33	1.01±0.17	0.20±0.08	<0.001
GI	2.06±0.30	1.10±0.23	0.52±0.20	<0.001
BOP (%)	1.89±0.33	0.65±0.20	0.14±0.04	<0.001
PPD (mm)	3.21±0.27	2.94±0.31	2.20±0.16	<0.001
CAL (mm)	1.93±0.15	1.91±0.15	1.90±0.16	0.412

PI: plaque index, GI: gingival index, BOP: bleeding on probing, PPD: probing pocket depth, CAL: clinical attachment level; * Longitudinal comparison (baseline vs. post-surgery)

Significant reductions in inflammatory markers were noted following IPT and surgical intervention. PI decreased from 2.29±0.33 at baseline to 1.01±0.17 post-IPT (p<0.05) and further to 0.20±0.08 post-surgery (p<0.05), indicating effective plaque control. Similarly, GI improved from 2.06±0.30 to 1.10±0.23 post-IPT and 0.52±0.2 post-surgery (p<0.05 for both). Initially recorded at 1.89±0.33, BOP declined to 0.65±0.2 after IPT and reached 0.14±0.04 post-gingivectomy/plasty (p<0.05), reflecting the resolution of gingival inflammation. PD decreased progressively

from 3.21±0.27 mm at baseline to 2.94±0.31 mm post-IPT and 2.2±0.16 mm post-surgery (p<0.05). In contrast, CAL remained stable throughout the study (1.93±0.15 mm at baseline vs. 1.90±0.16 mm post-surgery; p>0.05), suggesting no adverse impact on periodontal attachment.

Histopathological and Cytological Analysis

Exfoliative cytology revealed no morphological abnormalities or pathological changes in epithelial cells during the healing process. The SCI and KI were analyzed

to assess epithelial regeneration dynamics in test (Nd:YAG laser-treated) and control, (Table 2, Table 3). At baseline, SCI and KI were comparable between groups (SCI: 93.68 ± 1.2 vs. 93.46 ± 1.34 ; KI: 26.08 ± 3.66 vs. 26.38 ± 3.45 ; $p > 0.05$). Postoperatively, SCI in the control increased from 3.34 ± 0.68 on day 1 to 56.8 ± 4.75 by day 21 ($p < 0.05$), while the test group demonstrated a more pronounced

rise, reaching 75.76 ± 1.63 by day 21 ($p < 0.05$ vs. control). Similarly, KI in the control group rose from 1.08 ± 0.49 (day 1) to 8.78 ± 1.04 (day 21), whereas the test group exhibited accelerated keratinization, with KI increasing to 17.24 ± 0.96 by day 21 ($p < 0.05$). The findings indicate that Nd:YAG laser application enhanced epithelial regeneration and maturation compared to conventional techniques (Table 4).

Table 2. Superficial cell index (SCI) during healing					
Groups	Baseline	Day 1	Day 3	Day 7	Day 21
Control	93.68 ± 1.2	3.34 ± 0.68	30.2 ± 7.03	48.3 ± 5.89	56.8 ± 4.75
Nd:YAG	93.4 ± 1.34	11.04 ± 2.1	46.5 ± 2.87	58 ± 1.57	75.7 ± 1.63
P-value	0.752	<0.001	<0.001	<0.001	<0.001
*Vertical comparison (Control vs. Nd:YAG laser)					

Table 3. Keratinization index (KI) during healing					
Groups	Baseline	Day 1	Day 3	Day 7	Day 21
Control	26.08 ± 3.66	1.08 ± 0.49	3.18 ± 1.01	5.82 ± 0.99	8.78 ± 1.04
Nd:YAG	26.38 ± 3.45	1.96 ± 0.61	5.16 ± 0.6	8.56 ± 0.78	17.2 ± 0.96
P-value	0.891	<0.001	<0.001	<0.001	<0.001
*Vertical comparison (Control vs. Nd:YAG laser)					

Table 4. Comparison of clinical periodontal measurements at baseline, after IPT, and after gingivectomy/plasty			
Parameter	Timepoint	Mean±SD	P value
PI	Baseline	2.29 ± 0.33	
	After BPT	1.01 ± 0.17^a	$p < 0.05$ vs. Baseline
	After gingivectomy/plasty	0.20 ± 0.08^b	$p < 0.05$ vs. Baseline
GI	Baseline	2.06 ± 0.30	
	After BPT	1.10 ± 0.23^a	$p < 0.05$ vs. Baseline
	After gingivectomy/plasty	0.52 ± 0.20^b	$p < 0.05$ vs. Baseline
PPD	Baseline	1.89 ± 0.33	
	After BPT	0.65 ± 0.20^a	$p < 0.05$ vs. Baseline
	After gingivectomy/plasty	0.14 ± 0.04^b	$p < 0.05$ vs. Baseline
CAL	Baseline	3.21 ± 0.27	
	After BPT	2.94 ± 0.31^a	$p < 0.05$ vs. Baseline
	After gingivectomy/plasty	2.20 ± 0.16^b	$p < 0.05$ vs. Baseline
RBS	Baseline	1.93 ± 0.15	
	After BPT	1.91 ± 0.15	NS
	After gingivectomy/plasty	1.90 ± 0.16	NS
The clinical periodontal parameters, including Plaque Index (PI), Gingival Index (GI), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL), showed statistically significant improvements following both Basic Periodontal Therapy and subsequent gingivectomy/plasty procedures when compared to baseline values ($p < 0.05$). ^a indicates statistically significant difference from baseline after IPT ($p < 0.05$). ^b indicates statistically significant difference from baseline after Gingivectomy/Plasty ($p < 0.05$). NS: Not significant.			

DISCUSSION

The present study evaluated the histopathological effects of Nd:YAG laser application on wound healing following gingivectomy/gingivoplasty in individuals with chronic inflammatory gingival hyperplasia. Our findings strongly suggest Nd:YAG laser therapy can serve as a beneficial adjunct in gingival surgical procedures, accelerating wound healing and improving patient comfort postoperatively. It also provides strong evidence supporting the clinical utility of Nd:YAG lasers in periodontal interventions, with

potential implications for broader applications in soft tissue healing and regenerative medicine. Additionally, IPT improved clinical periodontal parameters in individuals with chronic inflammatory gingival hyperplasia.

Oral hygiene education (OHE) plays a pivotal role in controlling plaque accumulation and preventing the formation of microbial dental biofilms, the primary etiological factor for periodontal diseases (3,4). Consistent with previous literature, IPT and OHE remain the cornerstone of periodontal disease management.

IPT, including mechanical, manual, ultrasonic, and laser-assisted instrumentation, effectively removes microbial dental plaque and calcified by-products from the tooth and supporting tissues, thereby reducing oral microbial load and mitigating inflammatory burden when combined with OHE (5). In our analysis, following IPT, marked reductions in plaque accumulation and gingival inflammation were observed, consistent with established principles of microbial biofilm disruption and host modulation. The further decline in these parameters after surgical intervention suggests that gingivectomy/gingivoplasty addresses residual anatomical and inflammatory challenges not fully resolved by nonsurgical therapy alone. This aligns with evidence highlighting the complementary role of surgical contouring in eliminating plaque-retentive niches and optimizing the gingival microenvironment for long-term stability. Notably, the resolution of sulcular bleeding and improvement in CAL followed a parallel trajectory, with the most pronounced gains occurring after surgical therapy. These findings reinforce that mechanical debridement and inflammation control during IPT create a foundation for surgical success, while definitive tissue remodeling facilitates physiological adaptation and functional restoration.

The progressive nature of these improvements supports the hypothesis that a phased approach—targeting infection control before structural correction—maximizes therapeutic outcomes in complex periodontal cases. Collectively, these results emphasize the importance of integrating nonsurgical and surgical strategies to address both the microbiological and morphological dimensions of periodontal disease. Recent studies have highlighted the significance of initial PT in reducing clinical parameters such as PI, GI, and CAL in patients with gingival hyperplasia. For instance, a study by Burzlaff et al. demonstrated significant reductions in PI, GI, and CAL values six months after IPT in such patients (9). Similarly, another study by Ilgenli et al. reported that IPT significantly improved these clinical parameters after an 8-week follow-up (10).

A comparative study by Mavrogiannis et al. evaluated the efficacy of gingivectomy/plasty versus periodontal flap surgery and reported significant reductions in PI, GI, and CAL six weeks post-gingivectomy/plasty, corroborating our findings that surgical intervention further enhances periodontal outcomes (11). Despite the benefits of IPT, it is often insufficient for managing chronic inflammatory gingival hyperplasia with pseudo-pocket formation, necessitating adjunctive surgical interventions such as gingivectomy or periodontal flap surgery. Given the oral cavity's microbial burden, which poses a substantial risk to wound healing, adjunctive therapeutic agents have been explored. Various herbal and chemotherapeutic agents have been investigated for their wound-healing potential, but consensus remains elusive. In a study by Patel et al., ozonated oil applied to donor sites in free gingival graft procedures resulted in accelerated healing (12). Similarly, Tasdemir et al. reported improved wound healing and comfort following ozone therapy post-gingivectomy/

plasty (13). Additionally, Liu et al. reported enhanced tissue repair with ozone-based interventions in periodontal procedures (14). Our study employed a split-mouth design to control interindividual wound healing. The split-mouth methodology is well-established for periodontal studies, as it ensures similar healing conditions and enhances the reliability of comparative assessments (15).

It has been shown to modulate inflammatory responses by reducing pro-inflammatory cytokines such as TNF- α , IL-1 β , and COX-2, thereby promoting tissue repair and regeneration (16). Photobiomodulation enhances periodontal healing, yet the precise molecular mechanisms remain incompletely understood. Photobiomodulation influences mitochondrial activity at the cellular level, leading to increased ATP production and modulation of reactive oxygen species, critical for cell proliferation and differentiation (17). Furthermore, it has been reported to enhance the function of periodontal ligament stem cells, facilitating periodontal tissue regeneration (18). Despite these findings, there is a paucity of data elucidating the specific signaling pathways and gene expression profiles involved in photobiomodulation-mediated periodontal healing. Future research employing advanced molecular techniques is warranted to fully characterize these mechanisms, which could lead to optimized laser therapy protocols for periodontal regeneration (16-18).

Histopathological assessment of wound healing dynamics benefits from exfoliative cytology, a minimally invasive technique that permits serial evaluation without disrupting tissue repair—a methodological approach validated in investigations of post-surgical epithelialization (19,20). While baseline measures of epithelial integrity were comparable between groups, early postoperative phases revealed a transient decline in healing indices, consistent with expected inflammatory responses to trauma. Our findings align with these precedents, demonstrating progressive improvements in epithelial maturation across both study groups, though with a distinct advantage observed in sites treated with Nd:YAG. However, assessments documented accelerated recovery trajectories in laser-treated sites, with enhanced restoration of surface architecture and keratinocyte maturation by the observation endpoint (21). Nd:YAG laser application may modulate critical phases of wound repair, potentially through photobiomodulation effects that optimize cellular proliferation and reduce pro-inflammatory signaling (22). The differential outcomes between conventional and laser-augmented protocols underscore the therapeutic potential of adjunctive laser therapy in periodontal surgical care. These observations resonate with emerging evidence highlighting laser-mediated enhancements in soft tissue regeneration, though our study extends these principles to the context of post-gingivectomy recovery (22,23).

Our findings correlate well with recent reviews indicating enhanced postoperative healing with adjunctive Nd:YAG therapy. Specifically, Rossi and Romanos reported substantial reductions in inflammatory biomarkers and

accelerated epithelialization following Nd:YAG laser application, which aligns closely with our observations regarding improved SCI and KI (24). Furthermore, patient-centered outcomes such as reduced postoperative discomfort and improved patient satisfaction noted by Zou et al. emphasize the additional benefits provided by Nd:YAG lasers beyond histological improvements alone (25). This complementary evidence strengthens clinical relevance of our results and highlights the broader applicability of laser-assisted periodontal therapy in clinical practice. While our 21-day follow-up period demonstrated short-term benefits of Nd:YAG laser, longer-term follow-up is crucial for evaluating sustained outcomes. Previous studies suggest that extended observational periods of 6 to 12 months are necessary to fully assess stability and recurrence rates of gingival hyperplasia after periodontal interventions (26,27). Further molecular studies are required to better understand the precise mechanisms by which Nd:YAG enhances periodontal healing, including signaling pathways, gene expression profiles, and cellular responses. Recent research suggests involvement of specific cytokine modulations and mitochondrial functions, indicating potential areas for future investigations (28,29).

Our study has some limitations in that the sample size was relatively small, which may limit the generalizability of our findings. Additionally, our follow-up period was limited to 21 days, preventing an assessment of long-term histopathological outcomes. Future studies with larger cohorts and extended follow-up periods are warranted to validate our results. Moreover, while SHI and KI provided valuable insights, additional histopathological markers and molecular analyses could further elucidate the mechanisms underlying Nd:YAG laser-mediated wound healing.

CONCLUSION

Nd:YAG laser application following gingivectomy/plasty enhances wound healing, as evidenced by increased SHI and KI values in the laser-treated group. The accelerated healing process was associated with improved patient comfort and easier oral hygiene maintenance in the treated region. While our study supports the clinical utility of Nd:YAG laser therapy in periodontal surgery, further research is needed to elucidate its molecular mechanisms and optimize its application for enhanced wound healing outcomes.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: The study was approved by the Ethics Committee of Atatürk University Faculty of Dentistry (Meeting Date: 25.10.2017, Meeting No: 13/2017, Decision No: 82), and conducted in accordance with the provisions of the Regulation on Clinical Trials issued by the Ministry of Health of the Republic of Türkiye.

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Evaluation of Sociodemographic Characteristics, Psychiatric Comorbidities, and Self-Esteem in Adolescents Diagnosed with Obesity and Comparison with Control Group

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Abstract

Aim: The primary objective of this research was to investigate the sociodemographic profiles, prevalence of psychiatric comorbidities, and self-esteem levels among adolescents diagnosed with obesity, and to contrast these findings with those of a control group.

Material and Method: This study employed a cross-sectional design involving 30 obese adolescents and 28 age- and gender-matched participants without obesity, all between the ages of 11 and 18. Data collection instruments included a structured sociodemographic questionnaire, the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL), and the Rosenberg Self-Esteem Scale (RSES). Group comparisons were made using independent samples t-tests and chi-square tests, with statistical significance defined as $p < 0.05$.

Results: No statistically significant differences were identified between the groups regarding age, sex distribution, school grade level, or academic achievement. However, the body mass index (BMI) was markedly elevated in the obese group compared to controls ($p < 0.001$). Psychiatric diagnoses were significantly more frequent in the obesity group (60%) relative to the control group (32.1%) ($p = 0.034$), with mood disorders and multiple psychiatric diagnoses being notably prevalent. Despite this, there were no significant group differences in mean RSES scores or self-reported self-esteem levels ($p = 0.290$ and $p = 0.793$, respectively).

Conclusion: The findings underscore a higher rate of psychiatric comorbidity among adolescents living with obesity, suggesting that mental health evaluation and psychological support should be integral components of adolescent obesity prevention and intervention strategies.

Keywords: Adolescent obesity, psychiatric comorbidity, self-esteem

INTRODUCTION

Obesity is recognized as a long-standing medical condition marked by an abnormal accumulation of body fat, which occurs when energy consumption surpasses energy expenditure (1). The most frequently utilized metric to assess and categorize obesity is the body mass index (BMI), calculated by dividing an individual's weight by the square of their height in meters (kg/m^2) (2). According to the World Health Organization's classification, a BMI under 18.5 indicates underweight status, a value between 18.5–24.9 reflects normal weight, 25–29.9 is considered overweight, 30–34.9 defines class 1 obesity, 35–39.9 corresponds to class 2 obesity, and a BMI of 40 or more is classified as class 3 or morbid obesity (3).

Beyond its well-documented adverse effects on physical health, both obesity and overweight are linked to the emergence of psychiatric conditions. These weight-related issues have also been shown to negatively influence the quality of life in pediatric and adolescent populations (4). Extensive research has demonstrated that obesity in youth is strongly associated with reduced levels of perceived well-being and life satisfaction (5). Adolescents with obesity tend to report a greater number of somatic complaints (6), higher susceptibility to sleep-related difficulties (7), and an increased frequency of symptoms such as headaches, backaches, and gastrointestinal disturbances (8-10). Behavioral challenges are also more common, with studies

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indicating a higher prevalence of both internalizing symptoms (e.g., emotional withdrawal, anxiety) and externalizing behaviors (e.g., aggression, rule-breaking) in obese and overweight adolescents. Furthermore, it has been well documented that these individuals experience more peer-related difficulties compared to adolescents with a healthy body weight (11).

The psychological implications of obesity and excess weight in youth are broad, encompassing both general psychosocial difficulties and more clearly defined psychiatric diagnoses. Children and adolescents affected by obesity are known to be at heightened risk for a variety of mental health concerns, such as distorted body image, diminished self-esteem, social exclusion, interpersonal difficulties, weight-based discrimination and bullying, decreased health-related quality of life, depressive symptoms, and disordered patterns of eating (including binge eating, eating without hunger, and loss of control over intake), along with heightened anxiety and a marked increase in both internalizing and externalizing problems (12-16).

This study is designed to evaluate the sociodemographic profiles of adolescents clinically diagnosed with obesity, to identify co-occurring psychiatric disorders, and to explore how obesity may influence self-esteem levels within this population.

MATERIAL AND METHOD

Study Design and Sample

Ethical clearance for this research was granted by the Non-Interventional Clinical Research Ethics Committee of Karabük University, Republic of Türkiye (Approval No: 2025/2226; Approval Date: April 16, 2025). Prior to participation, written informed consent was secured from all adolescents and their legal representatives. This investigation employed a cross-sectional study design and was carried out within the Department of Child and Adolescent Psychiatry at Karabük Training and Research Hospital. The research commenced in March 2025, with participant enrollment occurring between March and April of the same year. Adolescents who met the clinical criteria for obesity, were making their initial visit to the Pediatric Outpatient Clinic during this timeframe, consented to take part, and were subsequently referred to the psychiatry department were enrolled in the study group. A control group was established using volunteers without obesity and who were age- and gender-matched to those in the obesity cohort.

The study population included adolescents aged between 11 and 18 years who had been referred from the pediatric outpatient services to the child and adolescent psychiatry outpatient clinic. Those in the control group were individuals with no diagnosis of obesity and were matched to the study group participants based on both gender and age.

Inclusion criteria:

- Presentation to the Pediatric Outpatient Clinic with a BMI over 30,
- Sufficient mental capacity to comprehend the study and cooperate,
- Voluntary participation and provision of written informed consent.

Exclusion criteria:

- Presence of a physical or mental disability that would interfere with comprehension or cooperation,
- Refusal to give informed consent for participation in the study.

During the study period, a sociodemographic data form was administered to collect descriptive information about the participants. Psychiatric diagnoses were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL). The Rosenberg Self-Esteem Scale (RSES) was also administered to the adolescents.

Data Collection Tools

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)

The original version of this semi-structured diagnostic interview, known as K-SADS-P, was developed by Chambers and colleagues in 1984 (17). Later, it was updated and refined by Kaufman et al. in 1997 to assess psychiatric conditions in both children and adolescents (18). The instrument is specifically intended for use with both the young individual and their caregiver. It encompasses five primary diagnostic domains—mood disorders, psychotic disorders, anxiety disorders, behavioral disorders, and substance-related disorders—along with additional submodules and a global functioning evaluation scale tailored for pediatric populations (18).

The assessment of the scale's reliability and validity within the Turkish context was carried out by Gökler and colleagues in 2004. The first section collects sociodemographic information, health status, current complaints, history of psychiatric treatment, and information about school performance, hobbies, and social relationships. In the second section, approximately 200 specific symptoms and behaviors are assessed through a diagnostic screening interview. The severity of symptoms is rated on a scale from 0 to 3. If positive symptoms are identified during the screening, follow-up questions related to the specific diagnostic domain are administered to confirm the diagnosis. Each supplemental symptom checklist includes screening items and criteria for evaluating the most severe current and past episodes, with additional scoring (19).

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria are used for each diagnosis. The third section, known as the general assessment scale for children, is used to evaluate the present functional status of the child. Regarding a study executed by Gökler et al., diagnoses established by child and adolescent psychiatrists (based on DSM-IV) showed statistically significant agreement with diagnoses obtained via K-SADS-PL interviews. Kappa values indicated excellent agreement for externalizing disorders, good agreement for attention deficit hiperactivity disorder (ADHD) and tic disorders, and moderate agreement for mood disorders, anxiety disorders, and obsessive-compulsive spectrum disorders (19).

Sociodemographic Data Form

A brief questionnaire was developed specifically for this study to assess variables such as age, gender, family structure, educational background, and history of psychiatric consultations.

Rosenberg Self-Esteem Scale

The RSES was employed in this study to assess the self-esteem levels of participating adolescents. Initially introduced by Morris Rosenberg in 1963 (20), the scale gained recognition for its psychometric robustness following validation and reliability testing in the United States and has since been extensively utilized in psychological research. The Turkish adaptation of the RSES underwent a validity and reliability assessment by Çuhadaroğlu, documented in his specialization thesis at the Hacettepe University Faculty of Medicine, Department of Psychiatry in 1986 (21). For this study, the assessment focused solely on the first 10 items of the self-esteem dimension, as adopted by Önder and colleagues in their research examining psychopathological indicators, quality of life, and parental behaviors in obese youth (22). According to the scoring criteria for the "Self-Esteem" subscale, a total score between 0 and 1 signifies high self-esteem, a score between 2 and 4 denotes moderate self-esteem, and a score from 5 to 6 indicates low self-esteem (21).

Statistical Analysis

Descriptive analyses were performed for all variables included in the study. Categorical data were summarized using frequencies (n) and corresponding percentages (%). Assessment of whether data conformed to a Gaussian distribution was conducted via the Kolmogorov–Smirnov procedure. Categorical comparisons across cohorts employed Pearson chi-square analyses, with Fisher's exact test substituting when expected cell counts were low. For interval data exhibiting normality, group means were contrasted using the independent-samples t-test. Statistical significance was defined at $p < 0.05$. All computations were executed in IBM SPSS Statistics for Mac (version 26.0; IBM Corp., Armonk, NY).

RESULTS

Sociodemographic and clinical data comparisons between the obese and control groups are displayed in Table 1. In the obesity group, there were 15 males and 15 females, while the control group consisted of 11 males and 17 females. The average age in the obesity group was 15.05 ± 2.21 years, and 14.35 ± 2.27 years in the control group. There were no statistically meaningful differences in gender or age distribution between the two cohorts ($p = 0.242$ and $p = 0.419$, respectively). As expected, BMI was markedly elevated in the obese group ($p < 0.001$). Educational level and school performance did not differ significantly between the groups ($p = 0.198$ and $p = 0.844$, respectively). Although higher rates of coexisting physical illnesses and medication usage were observed among the obese adolescents, these trends did not reach statistical significance ($p = 0.070$ and $p = 0.052$, respectively). Psychiatric diagnoses were found in 60% of the participants in the obesity group, while the prevalence was 32.1% in the control group, as illustrated in Figure 1. The difference in psychiatric comorbidity rates between the groups was significant ($p = 0.034$). No significant differences were noted between the groups in terms of RSES scores or levels of self-esteem ($p = 0.290$ and $p = 0.793$, respectively).

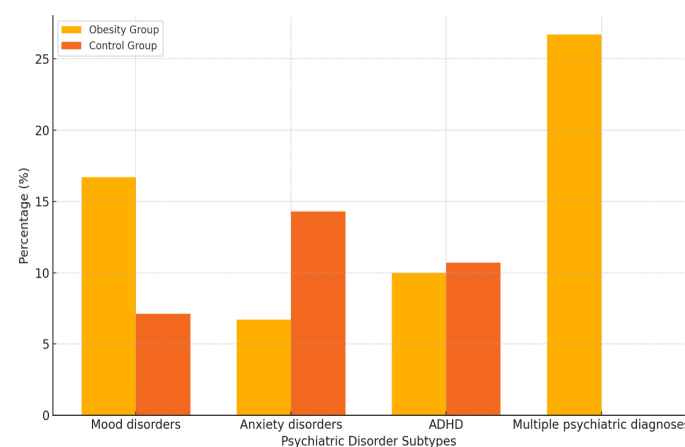


Figure 1. Psychiatric comorbidities in adolescents with and without obesity

Table 2 presents the comparison of family characteristics between the obesity and control groups. There were no statistically significant differences between the groups in terms of family type ($p = 0.187$), parental marital status ($p = 0.257$), number of siblings ($p = 0.601$), place of residence ($p = 0.732$), or family income level ($p = 0.355$).

Table 3 presents the comparison of parental sociodemographic and clinical characteristics between the obesity and control groups. No statistically significant differences were found between the groups in terms of maternal or paternal survival status, employment status, age, presence of psychiatric or organic illness, smoking or alcohol use, or education level.

Table 1. Comparison of sociodemographic and clinical data between the groups

	Obesity (n=30) n (%) or mean±std	Control group (n=28) n (%) or mean±std	p-value
Gender			0.419
Male	15 (50)	11 (39.3)	
Female	15 (50)	17 (60.7)	
Age, years	15.05±2.21	14.35±2.27	0.242
BMI, kg/m²	32.30±1.79	21.54±2.94	<0.001
Educational status			0.198
Middle school	10 (33.3)	14 (50)	
High school	20 (66.7)	14 (50)	
Academic performance			0.844
Excellent	4 (13.3)	5 (17.9)	
Good	14 (46.7)	12 (42.9)	
Average	8 (26.7)	6 (21.4)	
Poor	3 (10.0)	5 (17.9)	
Irregular attendance	1 (3.3)	0 (0)	
Presence of medical illness	9 (30)	3 (10.7)	0.070
Medication use	11 (36.7)	4 (14.3)	0.052
Psychiatric disorder	18 (60.0)	9 (32.1)	0.034
Mood disorders	5 (16.7)	2 (7.1)	
Anxiety disorders	2 (6.7)	4 (14.3)	
ADHD	3 (10.0)	3 (10.7)	
Multiple psychiatric diagnoses	8 (26.7)	0 (0)	
RSES	1.86±1.25	2.22±1.30	0.290
Self-esteem level			0.793
High	16 (53.3)	12 (42.9)	
Moderate	13 (43.3)	15 (53.6)	
Low	1 (3.3)	1 (3.6)	

The chi-square test and independent samples t-test were used; A p-value of less than 0.05 was considered statistically significant; BMI: body mass index, ADHD: attention deficit hyperactivity disorder, RSES: Rosenberg Self-Esteem Scale

Table 2. Comparison of family characteristics between the groups

	Obesity (n=30) n (%)	Control group (n=28) n (%)	p-value
Family type			0.187
Nuclear	29 (96.7)	24 (85.7)	
Extended	1 (3.3)	4 (14.3)	
Parental marital status			0.257
Together	26 (86.7)	21 (75.0)	
Separated	4 (13.3)	7 (25.0)	
Number of siblings			0.601
1	13 (43.3)	12 (42.9)	
2	11 (36.7)	8 (28.6)	
3	6 (20)	5 (17.9)	
4	0 (0)	2 (7.1)	
6	0 (0)	1 (3.6)	
Place of residence			0.732
Urban	24 (80.0)	24 (85.7)	
Rural	6 (20.0)	4 (14.3)	
Family income level			0.355
High	14 (46.7)	9 (32.1)	
Medium	10 (33.3)	9 (32.1)	
Low	6 (20.0)	10 (35.7)	

The chi-square was used. A p-value of less than 0.05 was considered statistically significant.

Table 3. Comparison of parental sociodemographic and clinical characteristics between the groups			
	Obesity (n=30) n (%) or mean±std	Control group (n=28) n (%) or mean±std	p-value
Mother			1.000
Alive	29 (96.7)	27 (96.4)	
Deceased	1 (3.3)	1 (3.6)	
Mother's employment status	9 (30.0)	12 (42.9)	0.309
Mother's age, years	41.93±5.11	41.50±6.61	0.780
Psychiatric illness in mother	4 (13.3)	1 (3.6)	0.354
Mood disorder	1 (3.3)	0 (0)	
Anxiety disorder	3 (10.0)	0 (0)	
OCD	0 (0)	1 (3.6)	
Organic disease in mother	9 (30.0)	4 (14.3)	0.152
Maternal smoking	10 (33.3)	13 (46.4)	0.308
Maternal alcohol use	2 (6.7)	0 (0)	0.492
Mother's education level			0.292
Illiterate	2 (6.7)	0 (0)	
Middle school	13 (43.3)	10 (35.7)	
High school	12 (40.0)	11 (39.3)	
University	3 (10.0)	7 (25.0)	
Father			0.605
Alive	29 (96.7)	26 (92.9)	
Deceased	1 (3.3)	2 (7.1)	
Father's employment status	24 (80.0)	20 (71.4)	0.446
Father's age, years	47.83±8.20	45.71±6.73	0.289
Psychiatric illness in father	4 (13.3)	1 (3.6)	1.000
Schizophrenia	1 (3.3)	1 (3.6)	
Organic disease in father	9 (30.0)	6 (21.4)	0.456
Paternal smoking	17 (56.7)	20 (71.4)	0.242
Paternal alcohol use	7 (23.3)	3 (11.1)	0.304
Father's education level			1.000
Middle school	13 (43.3)	11 (39.3)	
High school	12 (40.0)	12 (42.9)	
University	5 (16.7)	5 (17.9)	
The chi-square test and independent samples t-test were used. A p-value of less than 0.05 was considered statistically significant. OCD: Obsessive-compulsive disorder.			

DISCUSSION

Obesity in adolescence represents a multifaceted challenge that extends far beyond simple caloric imbalance. Obesity results from excessive caloric intake relative to expenditure. Numerous studies have also demonstrated its profound impact on psychological well-being and psychiatric comorbidity in youth (11-13).

First, epidemiological evidence underscores a strong association between obesity and mood and anxiety disorders. A large systematic review found that obese children and adolescents have significantly higher rates of both depression and anxiety compared to their normal-weight peers. Longitudinal data further suggest a bidirectional link: not only does obesity increase the risk of later depressive and anxiety symptoms, but early mood and anxiety disorders may also predispose to future weight gain (23).

Peer relationships are another domain severely affected by adolescent obesity. Overweight youth experience both overt and relational peer victimization, which leads to social isolation and poorer friendship quality (24,25). This social marginalization reinforces low self-esteem and body dissatisfaction, creating a vicious cycle wherein distress drives maladaptive coping, such as emotional or binge eating (26).

Obese adolescents consistently report lower self-esteem, a critical component of mental health. Meta-analytic data indicate a significant inverse relationship between BMI and RSES scores, with overweight youth reporting markedly lower global self-worth (27,28). Such diminished self-esteem not only contributes to depressive symptomatology but also impairs motivation for health-promoting behaviors, hindering effective obesity interventions.

Somatic complaints and functional impairments are likewise more prevalent among obese adolescents. Studies reveal that headaches, back pain, and gastrointestinal symptoms occur at higher rates in this group, even after controlling for organic pathology (29,30). These somatic symptoms often drive excessive healthcare utilization and may mask underlying psychological distress, complicating clinical management.

Sleep disturbances represent another important intersection of obesity and mental health. Although some studies suggest no baseline association between sleep restriction and obesity (31), others have demonstrated that obese adolescents report higher rates of insomnia, poor sleep quality, and daytime somnolence, which in turn exacerbate mood dysregulation and cognitive difficulties (32). Given the bidirectional links between sleep, mood, and weight regulation, addressing sleep hygiene is a crucial component of holistic treatment.

Behavioral and psychosocial difficulties, including both internalizing (e.g., withdrawal, anxiety) and externalizing (e.g., aggression, conduct problems) profiles, are elevated in obese youth (33). Such behavioral patterns often reflect broader deficits in emotion regulation and social competence, necessitating integrated interventions that target both weight and psychosocial functioning.

Finally, the role of lifestyle interventions in ameliorating both physical and mental health sequelae of obesity cannot be overstated. Emerging evidence from randomized trials indicates that multi-component lifestyle programs yield modest but significant improvements in depressive symptoms and quality of life among overweight and obese children and adolescents, even in the absence of substantial BMI reduction (34). These findings highlight the therapeutic value of combining nutritional guidance, physical activity promotion, and cognitive-behavioral strategies to foster sustainable change.

There are certain limitations associated with this research. Primarily, the cross-sectional methodology used restricts the capacity to determine definitive causal links between obesity and associated psychiatric disorders. Another notable limitation is the modest sample size, which may constrain the applicability of the results to larger, more diverse populations. Moreover, the use of self-administered instruments like the RSES introduces the possibility of bias stemming from participants' tendency to respond in socially acceptable ways. Furthermore, the investigation did not thoroughly explore other potentially influential factors—such as nutritional intake patterns, levels of physical activity, or detailed aspects of family environment—which may have played a role in shaping both psychological well-being and physical health indicators.

In sum, obesity in adolescence is intrinsically linked to a spectrum of psychiatric comorbidities—including mood and anxiety disorders, low self-esteem, peer relationship problems, somatic complaints, and sleep disturbances—

that collectively undermine quality of life and treatment engagement. Effective management requires a biopsychosocial approach that integrates weight-management interventions with targeted mental health support, peer and family involvement, and attention to sleep and somatic symptomatology.

CONCLUSION

In conclusion, this study highlights the increased prevalence of psychiatric comorbidities among adolescents diagnosed with obesity compared to their age- and gender-matched peers, despite no significant differences in self-esteem levels. These findings emphasize the importance of incorporating routine psychological assessment and mental health support into the clinical management of adolescent obesity. Addressing both physical and psychological dimensions is crucial for improving overall health outcomes and quality of life in this vulnerable population.

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Ethical approval: Ethical clearance for this research was granted by the Non-Interventional Clinical Research Ethics Committee of Karabük University, Republic of Türkiye (Approval No: 2025/2226; Approval Date: April 16, 2025). Prior to participation, written informed consent was secured from all adolescents and their legal representatives.

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Effect of Marginal Bone Resorption on Stress Distribution in Implants of Different Lengths: A Three-Dimensional Finite Element Analysis

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Abstract

Aim: Marginal bone resorption occurring around dental implants may cause biomechanical changes and lead to implant loss over time. It is not fully understood how this bone loss affects implants of different lengths and the stress on the surrounding bone.

Material and Method: Implant models with lengths of 6.6 mm and 13 mm were created at five different marginal bone resorption levels (0, 1, 2, 3 and 4 mm). All implants were 4.6 mm in diameter and were placed in idealized bone blocks with a crown representing the maxillary first molar. The models were analyzed under vertical and 30° oblique load of 100 newton (N). Von Mises stress in the implant body and maximum and minimum principal stress in cortical and cancellous bone were evaluated.

Results: The highest stress values were observed in 6.6 mm implants under oblique loading. While the von Mises stress was 97.4 megapascals (MPa) at 0 mm bone loss, it increased to 133.0 MPa at 4 mm bone loss. These values increased from 82 MPa to 99.1 MPa in 13 mm implants. The maximum principal stress in cortical bone increased from 13.7 MPa to 62.5 MPa in short implants and from 11.8 MPa to 36.0 MPa in long implants. Stress values were found to be higher in short implants at all resorption levels.

Conclusion: Implant length and level of bone loss affect stress distribution. Short implants and advanced resorption create more stress, while stress can be temporarily reduced by changing the load transmission geometry in the early stage.

Keywords: Finite element analysis, dental implants, bone resorption, alveolar bone loss

INTRODUCTION

Dental implants are a widely used treatment method today to restore the aesthetics and function of lost teeth, particularly in cases of single and partial tooth deficiencies, as they can be applied without damaging the neighboring teeth (1,2). The success of implant treatment is made possible by the osseointegration achieved between the titanium from which the implant is manufactured and the surrounding alveolar bone. Osseointegration is a stable form of connection in which the implant is directly united with the bone, without the presence of any intervening soft tissue. This connection is critically important for the long-term success of the implant and its ability to bear functional loads (3,4).

However, even if osseointegration has been achieved, marginal bone resorption around the implant may still

occur over time. This bone resorption may develop due to a variety of biological and biomechanical factors, such as surgical trauma, implant position, occlusal overload, implant-abutment connection type, plaque accumulation, infection, presence of a microgap, and soft tissue phenotype (5-7).

Albrektsson et al. (1986), based on the long-term follow-up results of Adell et al. (1981), proposed vertical bone loss as a criterion for evaluating implant success. Accordingly, in implants with successful osseointegration, a marginal bone loss of up to 1.5 mm during the first year and 0.2 mm in each subsequent year has been defined as the acceptable upper limit (8-10). However, when marginal bone loss progresses beyond these physiological limits, it causes the support tissue around the implant to decrease, negatively affecting the biomechanical load balance. Particularly in

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cases where bone loss reaches 1.5 mm or more, the stress concentrated at the implant–abutment interface may lead to structural deteriorations such as microcracks and the formation of microgaps, creating conditions favorable for bacterial leakage and thereby compromising the long-term success of the implant (11).

Long implants are considered biomechanically advantageous because they provide a larger bone implant surface area (12,13). However, in cases with insufficient bone height, the use of short implants has become increasingly common and is successfully implemented as an alternative to vertical bone augmentation (14,15). In contrast, when marginal bone loss occurs in short implants, it will result in more limited bone support compared to long implants, and stress accumulation in the bone and implant-neck region becomes more pronounced, especially under oblique forces. This predisposes the implant to complications such as implant fracture, abutment screw loosening, or progressive resorption of the surrounding bone. Therefore, preserving marginal bone support is of greater importance in short implants (16).

Finite element analysis (FEA) is an effective method that allows precise modeling of complex structures in the digital environment, thus analyzing the biomechanical behaviors of the implant, superstructure and surrounding bone that cannot be directly observed in the clinic. This method enables three-dimensional investigation and comparison of the mechanical effects caused by different implant designs and varying degrees of marginal bone loss (11,17,18).

The aim of this study is to evaluate the stress distributions in the bone and implant body of two implants with different lengths in the presence of different degrees of marginal bone resorption by using three-dimensional FEA. Our hypothesis is that, with increasing marginal bone loss, the stress intensity on both the surrounding bone and the implant structure will be higher in short implants compared to long implants.

MATERIAL AND METHOD

The stress distributions of two different NTA (Switzerland) implants with diameters of 4.6 mm, lengths of 6.6 mm and 13 mm in idealized bone models with different levels of marginal bone resorption were compared. A total of five different resorption levels were modeled: 0 mm (no resorption), 1 mm, 2 mm, 3 mm and 4 mm. These five bone conditions were modeled and evaluated separately for each implant length (Figure 1).

Idealized bone blocks were modeled as rectangular prismatic structures consisting of cortical (1 mm thickness) and cancellous layers. The dimensions of the block were defined as 27 mm height, 15 mm buccolingual width and 18 mm mesiodistal length. Implant geometries were created based on standard tessellation language (STL) files provided by the manufacturer and with

permissions for use, and modeling was performed using Blender 4.2 (Amsterdam, Netherlands) and SolidWorks (Dassault Systèmes, France) software. Crown designs were created in accordance with the anatomical morphology of the maxillary first molar, and the implant-abutment-crown complex was modeled as a single-piece structure.

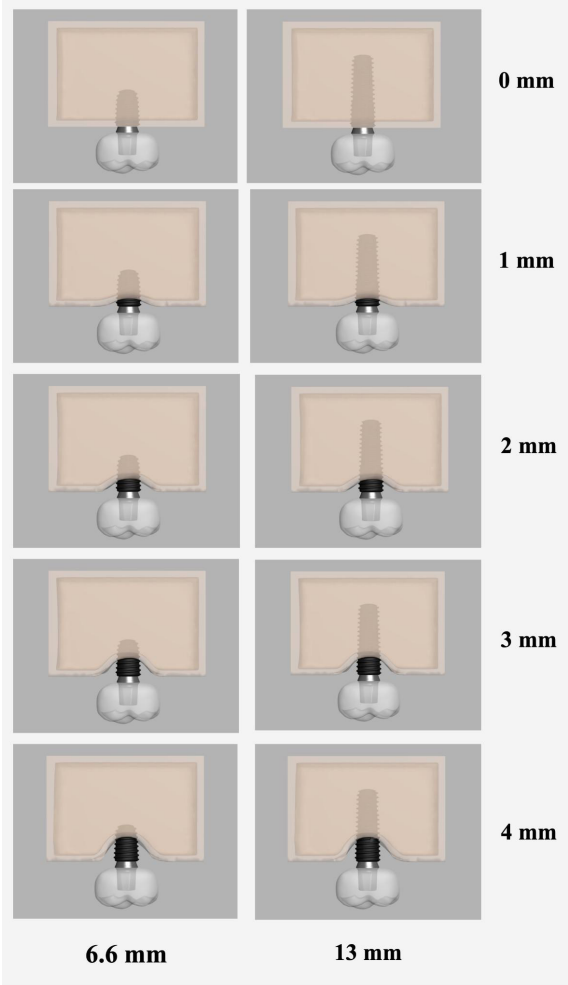


Figure 1. Finite element models of implants positioned in bone under varying levels of marginal bone resorption (0–4 mm) for 6.6 mm and 13 mm implant lengths

All structures are assumed to be isotropic, homogeneous and linearly elastic. The elastic modulus (Young’s Modulus) and Poisson ratios of the materials used are defined by reference to the values in the literature (19-21) (Table 1).

Table 1. Mechanical Properties of the Materials Used		
Material	Young’s Modulus (MPa)	Poisson’s Ratio
Cortical bone	13,700	0.30
Cancellous bone	1,370	0.30
Titanium	110,000	0.33
Porcelain	96,000	0.29

Meshing was performed using solid tetrahedral elements, with a denser mesh applied particularly in the implant–neck region. A fully osseointegrated condition (100% contact)

was assumed between the implant and the surrounding bone, and these interfaces were defined as rigid. Fixed boundary conditions were applied to the bottom and lateral surfaces of the bone blocks. The number of elements and nodes for each implant length and marginal bone resorption level is presented in Table 2.

Table 2. Number of elements and nodes in each model according to implant length and marginal bone resorption depth			
Implant length	Resorption level (mm)	Number of elements	Number of nodes
6.6 mm	0	450,484	109,945
	1	452,437	110,489
	2	452,405	110,323
	3	452,063	110,353
	4	453,914	110,683
13 mm	0	480,848	117,402
	1	484,533	118,178
	2	483,152	117,869
	3	484,334	118,164
	4	482,788	117,935

Two different loading scenarios were defined for each model. In the first case, a static vertical load of 100 newton (N) was applied perpendicular to the occlusal surface. In the second case, a force of 100 N was applied obliquely at an angle of 30° to the long axis of the implant. The loads were distributed homogeneously over the large contact area.

Analyses were performed using SIMULIA Abaqus (Dassault Systèmes, France) software. Maximum von Mises stress values were calculated in the implant body; maximum principal (tensile) and minimum principal (compression) stress distributions were analyzed separately in the cortical and cancellous bone regions.

This study was conducted entirely in a digital environment and does not contain any live data, patient images or personal health information. For these reasons, ethics committee approval is not required.

RESULTS

Von Mises Stress Values

Under vertical loading, the von Mises stress in the 6.6 mm implant was calculated as 25.60 megapascals (MPa) at 0 mm resorption, increasing to 26.90 MPa at 4 mm resorption, corresponding to a 5.1% increase. Under the same conditions, this value in the 13 mm implant increased from 19.60 MPa to 20.30 MPa, showing a 3.6% increase.

Under oblique loading, the von Mises stress in the 6.6 mm implant increased from 97.40 MPa at 0 mm resorption to 133.00 MPa at 4 mm resorption, corresponding to a 36.6% increase. In the 13 mm implant, under the same loading condition, the von Mises stress increased from 82.00 MPa to 99.10 MPa, representing a 20.9% increase (Table 3, Figure 2).

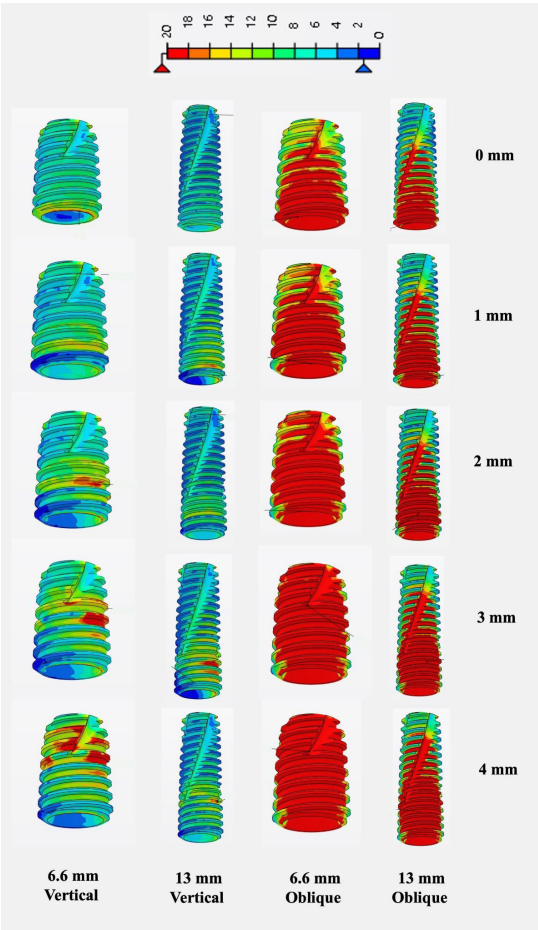


Figure 2. Von Mises stress distributions in the implants at varying levels of marginal bone resorption under vertical and oblique loading

Table 3. Maximum Von Mises Stresses (MPa) in the implant body according to resorption level			
Loading direction	Implant length	Resorption (mm)	Von Mises Max (MPa)
Vertical	6.6 mm	0	25.6
		1	21.0
		2	22.5
		3	28.5
		4	26.9
	13 mm	0	19.6
		1	23.0
		2	19.5
		3	23.3
		4	20.3
Oblique	6.6 mm	0	97.4
		1	86.7
		2	87.4
		3	105.0
		4	133.0
	13 mm	0	82.0
		1	79.2
		2	80.3
		3	88.7
		4	99.1

Principal Stresses (Cortical Bone)

Under vertical loading, the maximum principal stresses in the cortical bone increased from 6.73 MPa to 16.10 MPa in the 6.6 mm implant, corresponding to a 139.2% increase. In the 13 mm implant, this value increased from 3.42 MPa to 5.84 MPa, representing a 70.8% increase.

Under oblique loading, the maximum principal stress in the cortical bone for the 6.6 mm implant rose from 13.70 MPa to 62.50 MPa, indicating a 356.2% increase. In the 13 mm implant, the same parameter increased from 11.80 MPa to 36.00 MPa, showing a 205.1% rise.

The minimum principal stresses also accumulated in the same cortical regions and increased with the depth of resorption. Under vertical loading, the minimum principal stress in the 6.6 mm implant increased from -11.80 MPa to -18.20 MPa, corresponding to a 54.2% increase; in the 13 mm implant, it rose from -6.66 MPa to -8.45 MPa, indicating a 26.9% increase.

Under oblique loading, the minimum principal stress in the cortical bone for the 6.6 mm implant increased from -11.8 MPa to -18.2 MPa, reflecting a 54.2% increase. In the 13

mm implant, this value rose from -6.6 MPa to -8.45 MPa, reflecting a 28% increase (Table 4, Figure 3).

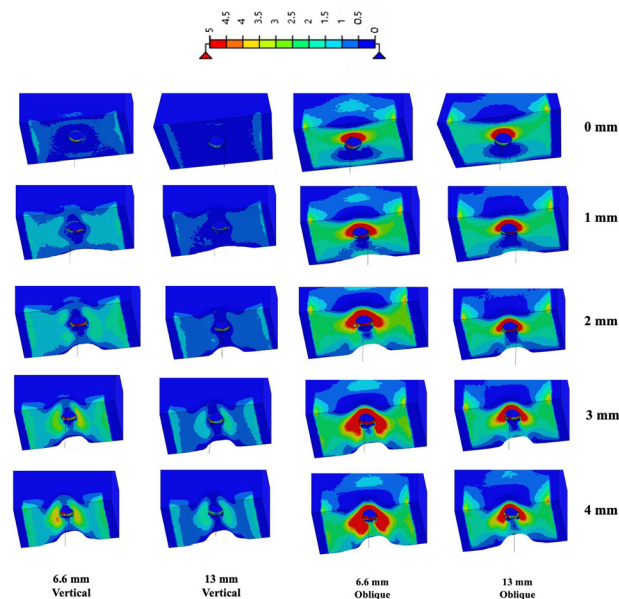


Figure 3. Maximum principal stress distributions in the cortical bone surrounding the implants at different levels of marginal bone resorption

Table 4. Maximum and minimum principal stress values (MPa) in cortical bone according to resorption level						
Loading direction	Implant length	Resorption (mm)	Maximum principal		Minimum principal	
			Max (MPa)	Min (MPa)	Max (MPa)	Min (MPa)
Vertical	6.6 mm	0	6.73	-2.62	1.07	-11.8
		1	9.89	-2.49	1.15	-13.7
		2	9.72	-2.7	1.08	-17.9
		3	11.3	-3.64	1.42	-13.5
		4	16.1	-4.8	1.59	-18.2
	13 mm	0	3.42	-2.14	0.25	-6.66
		1	5.74	-2.3	0.47	-11.0
		2	4.93	-1.86	0.49	-8.65
		3	5.5	-1.96	0.7	-8.61
		4	5.84	-1.8	0.65	-8.45
Oblique	6.6 mm	0	13.7	-6.37	1.07	-11.8
		1	21.0	-9.01	1.15	-13.7
		2	25.0	-11.1	1.08	-17.9
		3	47.2	-14.6	1.42	-13.5
		4	62.5	-19.6	1.59	-18.2
	13 mm	0	11.8	-4.49	0.25	-6.66
		1	16.7	-6.12	0.47	-11.0
		2	20.1	-8.05	0.49	-8.65
		3	26.7	-7.98	0.7	-8.61
		4	36.0	-10.2	0.65	-8.45

Principal Stresses (Cancellous Bone)

In cancellous bone, the maximum principal stresses reached higher values under oblique loading conditions.

In the 6.6 mm implant, this stress increased from 3.70 MPa to 5.23 MPa, corresponding to a 41.4% increase; in the 13 mm implant, it increased from 1.87 MPa to 3.09 MPa, indicating a 65.2% increase.

The minimum principal stresses were measured at lower levels but still showed a marked increase under oblique loading. In the 6.6 mm implant, the stress increased from -2.95 MPa to -5.51 MPa, reflecting an 86.8% rise; in the 13 mm implant, it rose from -1.62 MPa to -2.02 MPa, showing a 24.7% increase (Table 5, Figures 4, 5).

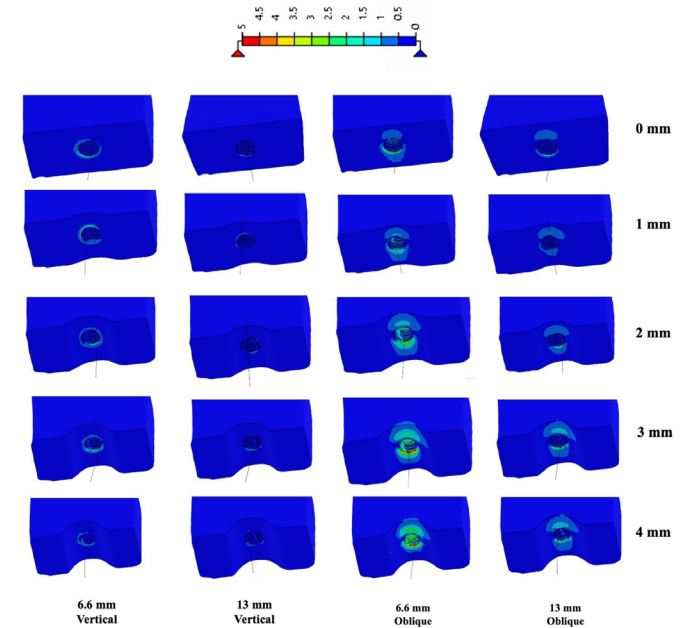


Figure 4. Maximum principal stress distributions in the cancellous bone surrounding the implants at different levels of marginal bone resorption

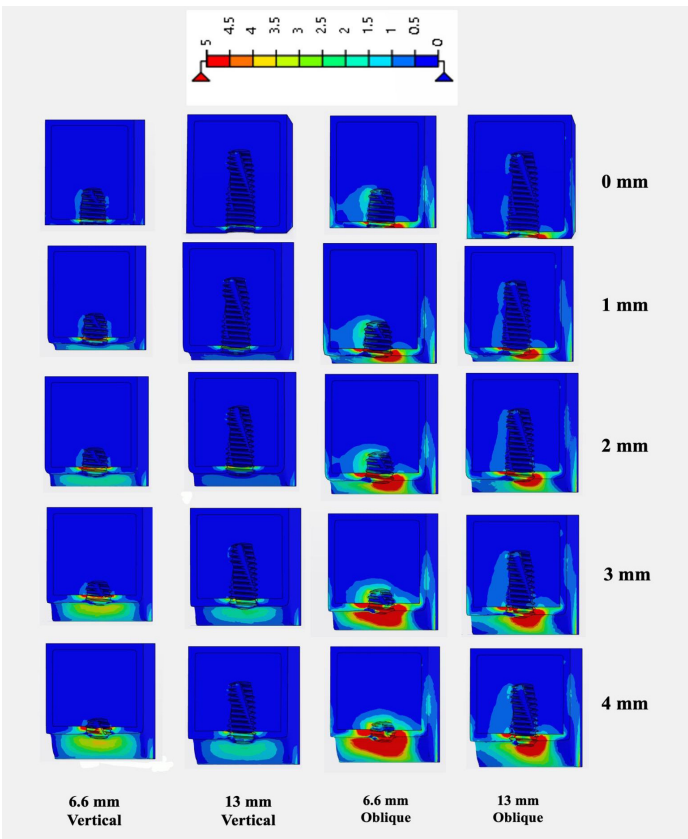


Figure 5. Maximum principal stress distributions in cortical and cancellous bone at various levels of marginal bone resorption (sectional view)

Table 5. Maximum and Minimum Principal Stress Values (MPa) in Cancellous Bone According to Resorption Level						
Loading direction	Implant length	Resorption (mm)	Maximum principal		Minimum principal	
			Max (MPa)	Min (MPa)	Max (MPa)	Min (MPa)
Vertical	6.6 mm	0	1.85	-0.52	0.56	-2.02
		1	2.04	-0.56	0.59	-2.07
		2	1.33	0.53	0.32	-2.11
		3	2.21	-0.53	0.47	-2.19
		4	1.34	-0.51	0.15	-2.07
	13 mm	0	0.83	-0.53	0.24	-1.75
		1	0.94	-0.55	0.27	-1.83
		2	0.9	-0.44	0.11	-1.58
		3	1.44	-0.47	0.34	-1.65
		4	1.29	-0.51	0.19	-1.72
Oblique	6.6 mm	0	3.7	-0.32	0.97	-2.95
		1	3.02	-0.37	0.16	-3.33
		2	3.47	-0.44	0.65	-3.85
		3	6.57	-0.29	1.24	-4.74
		4	5.23	-0.37	0.18	-5.51
	13 mm	0	1.87	-0.47	0.42	-1.62
		1	1.17	-0.47	0.1	-1.91
		2	1.36	-0.38	0.11	-1.87
		3	4.26	-0.37	0.86	-2.02
		4	3.09	-0.29	0.22	-2.02

DISCUSSION

In this study, the stress distributions of dental implants with two different lengths (6.6 mm and 13 mm) at five different marginal bone resorption levels (0, 1, 2, 3 and 4 mm) were evaluated by three-dimensional FEA. The findings showed that implant length and resorption amount had significant effects on both the von Mises stresses in the implant body and the principal stress distributions in cortical and cancellous bone.

At each resorption level, the stress values occurred in the 6.6 mm long short implant were found to be higher compared to the 13 mm long implant; also, the stress increase rate observed with increasing bone resorption was more pronounced in short implants. While the von Mises stress in the 6.6 mm implant under oblique loading was 97.4 MPa at 0 mm resorption, this value increased to 133.0 MPa at 4 mm bone resorption (36.6% increase). Under the same condition, the stress in the 13 mm implant increased by 20.9%, from 82 MPa to 99.1 MPa. The maximum principal stress increase in the cortical bone also showed a similar trend; This value increased from 13.7 MPa to 62.5 MPa (356.2%) for the 6.6 mm implant and from 11.8 MPa to 36.0 MPa (205.1%) for the 13 mm implant.

Similarly, in the FEA study conducted by Romeed et al. (2013), where they modeled marginal bone resorption at different levels on a 13 mm long implant, it was shown that the abutment screw was the region where the highest stress was concentrated and that the maximum stress was observed at the screw/implant connection, especially when the bone support was at the level of 10 mm, but that the stresses on the abutment screw decreased significantly, especially under oblique and vertical loading, when the bone support increased to 11.5 mm (22). Again, in the FEA study conducted by Lin et al. (2022), it was reported that the von Mises stress increased significantly in the implant screw and abutment connection regions as the marginal bone loss exceeded 1.5 mm. Especially in the external hexagon connection system, when the bone loss progressed from 3 mm to 5 mm, the stress on the screw increased by more than 25% and this stress exceeded the yield limit of the Ti-6Al-4V alloy, creating a potential risk of screw loosening or fracture (11).

Kitamura et al. (2005), in their study evaluating the effects of marginal bone loss on stress distribution, showed that the maximum von Mises stress observed in cortical bone, especially under oblique loading, increased with bone resorption depth in 1.3 mm and 2.6 mm bone loss scenarios (23). In the study, the maximum stress measured in cortical bone in the case of 2.6 mm horizontal resorption increased approximately 5 times compared to the model without bone loss. In addition, it was emphasized that the stress in cortical bone against oblique loads was 2 to 4 times higher than under axial loading. This finding of Kitamura et al. is also consistent with the findings of our study; in fact, the maximum principal stress in cortical bone at the level of 0 mm bone resorption in a 6.6 mm implant was measured as 6.73 MPa in vertical loading, while it was 13.7 MPa in oblique loading and increased

approximately 2 times. In the same implant, in the case of 4 mm resorption, the stress, which was 16.1 MPa in vertical loading, increased approximately 3.9 times to 62.5 MPa in oblique loading. Similarly, Akça and Çehreli (2006) showed that the displacement and elastic stress equivalent in the trabecular bone in contact with the implant neck increased significantly in simulations of progressive bone loss and oblique load (24).

In our study, contrary to expectations, a decrease in von Mises stress values was observed in the implant body during the early stages of marginal bone resorption (1 and 2 mm) in both short and long implant models. Under oblique loading, the von Mises stress in the 6.6 mm implant decreased from 97.4 MPa in the absence of resorption to 86.7 MPa and 87.4 MPa at 1 mm and 2 mm resorption levels, respectively. Similarly, in the 13 mm implant, no significant change in stress values was observed at these early resorption levels. This situation may result from the more angular connection of the cortical bone to the implant as resorption progresses in the early stages. Such angular contact may cause the cortical bone to wrap around the implant surface over a longer vertical distance. In addition, when the cortical bone approaches the implant body at an angle, the load transmission occurs on a longer cortical bone since the cortical bone surface will be the hypotenuse of the triangular area formed. This geometry may prevent stress concentration in a specific region and exert a stress-reducing effect on the implant. Another possibility is that the resorption line corresponds to different cross-sections of the implant's thread geometry. For instance, resorption at the 2 mm level may coincide with a narrower segment of the implant, leading to a more localized stress concentration; whereas at the 3 mm level, bone support aligning with a wider thread geometry may allow for more effective load distribution. Indeed, the observation in our study that stress under vertical loading at 4 mm resorption is lower than at 3 mm supports this possibility. Ultimately, such geometric differences may explain the non-linear behavior of stress values measured at different resorption levels.

Inglam et al. (2010) also reported in their FEA study on maxillary grafted sinus that similar strain energy density (SED) values were observed in cortical, cancellous and grafted bone regions in the case of 1.3 mm bone loss, indicating that the load was shared equally between the bone tissues. It was also reported that SED values in cortical bone at this level were lower than in models without bone loss (21). Although this study did not directly examine the stress distribution in the implant body, this balance in load sharing indicates that the stress occurring in the implant body in the early period may be limited.

There are some limitations to this study. First of all, the models we used in the FEA were created with idealized homogeneous and isotropic material properties and cannot fully reflect the biological, morphological and mechanical properties of real bone tissue. Cortical bone thickness was kept constant in all models, however, changes in cortical bone thickness may occur with resorption, which

may affect stress distribution. In addition, all analyses were performed under static loading and dynamic forces formed during chewing could not be evaluated. For these reasons, caution should be exercised when correlating the study results with clinical applications.

CONCLUSION

The findings showed that implant length, marginal bone resorption level and loading direction significantly affect the stress distribution in the implant and surrounding bone tissues. Especially in the short implant preference and in the 3 and 4 mm bone resorption scenarios, the stress values were found to be higher. In contrast, in the 1 and 2 mm bone resorption, a temporary decrease was observed in the von Mises stress values in the implant body. In addition, it was observed that the loads applied in the oblique direction created higher stress in both the implant and the bone compared to the vertical loading. In conclusion, not only the existing bone height but also the possible bone loss levels should be taken into account in implant planning.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: This study was conducted entirely in a digital environment and does not contain any live data, patient images or personal health information. For these reasons, ethics committee approval is not required.

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Gustave Roussy Immune Score in Nivolumab Treated Metastatic Renal Cell Carcinoma

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Abstract

Aim: The aim of this study is to evaluate the Gustave Roussy immune (GRIIm) score as a biomarker for survival in metastatic renal cell carcinoma (mRCC) patients receiving nivolumab following first-line treatment.

Material and Method: 41 mRCC patients who were given nivolumab beyond first line were included in this retrospective study. Data on ratio of neutrophile to lymphocyte, albumin, and LDH levels were utilized to determine GRIIm score. Patients scoring 2–3 were grouped into the high GRIIm score, whereas those scoring 0–1 were grouped as the low GRIIm score. The association between the GRIIm score and progression-free survival (PFS) with overall survival (OS) was examined.

Results: Thirty patients exhibited a low GRIIm score, whereas eleven presented a high GRIIm score. Prolonged median PFS and OS, with values of 7.06 months compared to 2.89 months ($p=0.002$) and 20.34 months compared to 4.27 months ($p<0.001$), are found respectively in low GRIIm score group. In terms of PFS, a higher GRIIm score was identified as an independent prognostic indicator but lacked prognostic significance for OS in multivariable analysis.

Conclusion: The GRIIm score may be used as an accessible and cost-effective prognostic biomarker in mRCC patients receiving nivolumab, and may assist clinicians in patient selection, thus improving therapeutic efficacy and the efficient use of clinical resources.

Keywords: Renal cell carcinoma, metastatic, Gustave Roussy immune score, nivolumab, prognosis

INTRODUCTION

There have been major changes in how metastatic renal cell carcinoma (mRCC) is treated in the last 20 years. One of the pivotal advancements was the tyrosine kinase inhibitors, they extended progression free survival (PFS) and became a standard treatment during the 2000s (1,2). However, despite initial efficacy, the majority of patients eventually develop resistance to vascular endothelial growth factor (VEGF)-targeted therapies, prompting the exploration of immune checkpoint inhibitors (ICIs) as an alternative treatment strategy. Nivolumab was the first ICI licensed for mRCC after the phase III CheckMate-025 study showed improved survival rates (3). Standard first-line treatment among all the risk groups of International Metastatic RCC Database Consortium (IMDC) have recently become ICI-based combination therapies. These therapies have shown significant benefits for patients with

intermediate-poor prognostic features (4,5).

Following Vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) failure, nivolumab is considered as an alternative therapeutic option (6). In Türkiye, clinical practice is shaped by national reimbursement policies, which currently authorize the use of nivolumab beyond first line treatment following VEGFR-TKI failure. This means that most of the real-world data show how nivolumab worked for people who had already failed TKI treatment. However, only a subset of these patients experience durable clinical benefit, underscoring the need for robust biomarkers that can predict response to ICIs (7,8).

Readily available markers derived from routine blood tests have garnered interest as potential predictors of immunotherapy outcomes in various cancers, including mRCC (9-12).

CITATION

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The Gustave Roussy immune (GRIIm) score is a composite indicator based on neutrophil to lymphocyte ratio, albumin, and LDH values (13). While the GRIIm score has shown prognostic relevance in several malignancies including lung cancers and gastrointestinal tumors, evidence regarding its utility in mRCC remains limited (14-19).

In this study, the GRIIm score's significance on prognosis in patients treated with nivolumab is evaluated, its potential role in stratifying patients based on anticipated clinical benefit from ICI therapy is emphasized.

MATERIAL AND METHOD

Data Collection

Patients with mRCC treated with nivolumab beyond the first line at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 1, 2017, and January 1, 2023 were included in this retrospective analysis. The review of electronic medical records provided data on demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), IMDC risk group, line of nivolumab therapy, time to disease progression, and time to death from the initiation of treatment. This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2023-09/80, Date: September 14, 2023).

GRIIm Score Calculation

GRIIm score was calculated with three peripheral blood markers: NLR, serum albumin concentration, and LDH. The scoring system was defined as follows:

- **Serum albumin:** ≤35 g/L =1 point; >35 g/L =0 point
- **LDH:** >220 IU/L =1 point; ≤220 IU/L =0 point
- **NLR:** >75th percentile of the cohort =1 point; ≤75th percentile =0 point
- **GRIIm score:** low group: 0 or 1 points
- **GRIIm score:** high group: 2 or 3 points (15).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 is used. Continuous variables were described as mean±standard deviation (SD). Frequencies and percentages summarized categorical variables. PFS and overall survival (OS) were explored using Kaplan Meier analysis. Prognostic factors are described with Cox regression models. Statistical significance was defined as a two-sided p-value less than 0.05 for all tests.

RESULTS

41 mRCC patients received nivolumab beyond first line were included. Most patients were male (n=34, 82.9%), while 7 patients (17.1%) were female. At treatment initiation, 32 patients (78%) had ECOG PS 1, and 9 patients (22%) had ECOG PS 2. The median age was 63 years (range: 37–86). Nivolumab was administered in second-line in 25 patients (61%) and in third-line in 16 patients (39%). 31 patients

(75.6%) were in the intermediate, 6 (14.6%) were in the poor, and 4 (9.8%) in the favorable IMDC risk group. Based on the GRIIm score, 30 patients (73.2%) were classified into the low GRIIm group (score 0–1), while 11 patients (26.8%) were in the high GRIIm group (score 2–3). Disease progression was observed in 35 patients (85.4%). A total of 33 patients (80.5%) had died, whereas 8 patients (19.5%) were alive at the last follow-up.

A statistically significant moderate positive correlation was observed between IMDC risk classification and GRIIm score grouping, as determined by Spearman's rank correlation analysis ($r_s=0.505$, $p=0.001$, $n=41$).

Median PFS was 7.06 months (95% CI: 1.99–12.13) vs 2.89 months (95% CI: 1.93–3.85) ($p=0.002$) between low and high GRIIm groups respectively (Figure 1). Median OS was 20.34 months (95% CI: 5.57–35.11) in the low GRIIm group compared to 4.27 months (0–8.95) in the high group ($p<0.001$) (Figure 2).

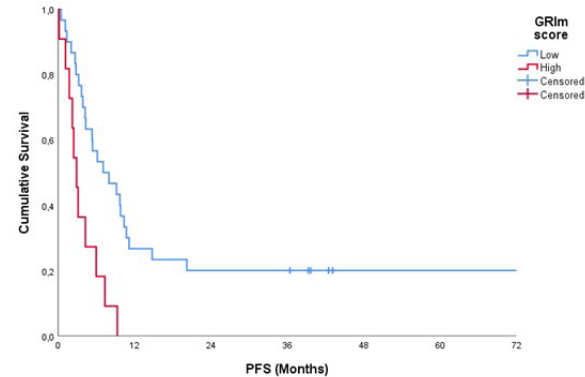


Figure 1. Kaplan–Meier analysis of PFS based on GRIIm score classification (low vs high)

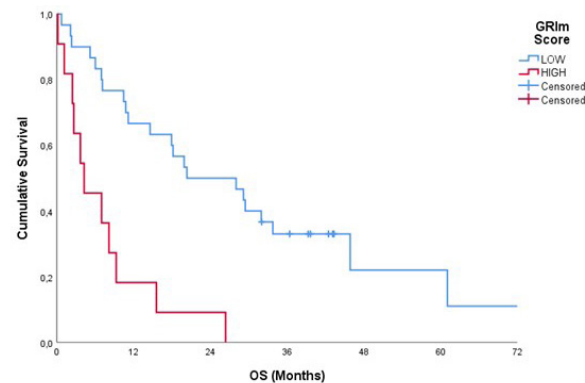


Figure 2. Kaplan–Meier analysis of OS based on GRIIm score classification (low vs high)

According to univariate analyses ECOG performance status, IMDC risk classification, and GRIIm score were significantly related to both PFS and OS. High GRIIm group exhibited a significantly reduced median PFS of 2.9 months compared to 7.06 months in the low GRIIm group ($p=0.002$). Similarly, OS was markedly reduced within high GRIIm group, with a median of 4.27 months versus 20.34 months in the low GRIIm group ($p<0.001$). In multivariate analysis, the GRIIm score was the sole significant independent predictor for PFS ($p=0.003$) (Table 1).

Table 1. Univariate and multivariate cox regression analyses for PFS and OS								
Variable	Univariate PFS Median (95% CI)	p value	Univariate OS Median (95% CI)	p value	Multivariate PFS HR (95% CI)	Multivariate PFS p-value	Multivariate OS HR (95% CI)	Multivariate OS p-value
Sex								
Female	9.17 (4.4–13.9)	0.27	18.17 (3.0–33.3)	0.57	-	-	-	-
Male	4.34 (2.7–5.98)		14.59 (4.48–24.7)					
Age								
≤63 years	5.40 (0.97–9.8)	0.90	18.17 (2.3–34.0)	0.45	-	-	-	-
>63 years	5.30 (1.8–8.9)		7.13 (4.67–9.59)					
ECOG PS								
0–1	6.10 (3.7–8.9)	0.06	18.17 (0.9–35.0)	0.01*	1.47 (0.64-3.4)	0.37	2.09 (0.8-5.5)	0.134
2–3	3.10 (1.1–5.1)		3.68 (0.7–6.65)					
IMDC score								
Favorable	7.10 (0–20.8)	0.045*	29.47 (15.8–43.1)	0.012*	0.82 (0.26-2.59)	0.74^60	0.81 (0.24-2.74)	0.52774^
Intermediate	5.40 (2.0–8.7)		15.58 (6.5–24.59)					
Poor	0.24 (1.76–2.7)		2.66 (0.45–8.87)					
Line of therapy								
2nd line	4.23 (2.52–5.95)	0.18	10.77 (4.6–16.96)	0.36	-	-	-	-
≥3rd line	7.32 (1.14–13.5)		18.17 (13.4–22.8)					
GRIIm score								
Low	7.06 (2.0–12.0)	0.002*	20.34 (5.57-35.1)	<0.001*	0.31 (014-0.67)	0.003*47*	0.34 (0.11-1.1)	0.06473
High	2.90 (1.9–3.8)		4.27 (0–8.9)					
*Significant, ^Poor vs Favorable								

DISCUSSION

We investigated the usefulness of the GRIIm score as a prognostic indicator in mRCC patients undergoing nivolumab treatment beyond first-line settings. We found a significant association between a high GRIIm score and decreased PFS. Notably, the GRIIm score was independently associated with PFS in multivariate analysis, highlighting its potential role in risk stratification for mRCC patients receiving immune checkpoint inhibitors. Although the GRIIm score was significantly associated with PFS in both univariate and multivariate analyses, its association with OS did not reach statistical significance in the multivariate model. This may be attributed to the limited sample size and potential confounding effects of post-progression treatments and other non-tumor-related factors that influence OS.

The GRIIm score, which combines serum albumin, LDH, and NLR, was originally developed as a simple immune-inflammatory biomarker to predict outcomes in patients treated with ICIs (13). These results support previous evidence demonstrating that systemic inflammation-based indicators like NLR and LDH have prognostic relevance in mRCC (20-22). High NLR levels have repeatedly been accompanied by unfavorable outcomes in patients receiving ICIs. Similarly, low albumin levels and increased LDH are indicative of malnutrition, high tumor burden, and metabolic stress, all of which are linked to poor clinical outcomes.

In this study population, a higher GRIIm score was linked to unfavorable prognosis, as evidenced by notably lower median PFS and OS in the high-risk category. These results highlight the GRIIm score's practical utility as a low-cost, non-invasive biomarker that can be easily integrated into daily oncology practice, particularly in settings where molecular profiling is unavailable or resource-limited. GRIIm score may complement existing risk models, such as the IMDC classification, by providing additional biologically relevant information derived from systemic inflammation and nutritional status.

While the implications of this study are encouraging, its retrospective and single-center design, along with the small sample size, may reduce the extent to which the findings can be generalized. Additionally, our analysis excluded patients treated with contemporary first-line ICI combinations, which have become standard care in many settings. Validation of these results in future multicenter, prospective cohorts is essential to fully establish the GRIIm score's predictive capacity in varied oncologic treatment landscapes.

CONCLUSION

The GRIIm score functions as a practical survival biomarker for mRCC patients receiving nivolumab after first-line treatment. In this retrospective cohort, a high GRIIm score had a significant association with reduced progression-free survival and overall survival. It continued to serve as an independent predictor of PFS in the multivariate analysis; however, no statistically significant association was found with OS.

These findings support the GRIIm score's potential role in clinical risk stratification and point out the need for further validation in broader, prospective studies.

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Evaluation of Pancreatic Injury in COVID-19 Patients: A Single Center Retrospective Study

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Abstract

Aim: Pancreatic injury has become a significant complication linked to COVID-19 infection. Our study's aim was to compare the clinical and laboratory findings, intensive care requirements, and mortality rates between patients with and without pancreatic enzyme elevation among those diagnosed with COVID-19.

Material and Method: The retrospective investigation was carried out at a tertiary hospital and involved PCR-confirmed COVID-19 patients. Data from 457 participants was collected, and 376 eligible participants were analyzed using statistical methods. Patients with amylase or lipase levels up to three times normal were classified as having pancreatic injury, while those with normal levels were the control group. Mann-Whitney U test was utilized for group comparisons. Factors predicting intensive care unit (ICU) admission were identified using logistic regression analysis; $p < 0.05$ is considered statistically significant.

Results: The study involved 376 participants (50 with pancreatic injury and 326 without). Patients with pancreatic injury experienced longer durations of antibiotic therapy ($p = 0.009$), extended hospital stays ($p = 0.018$), and higher rates of ICU admissions within the first week ($p = 0.045$). Biochemically, levels of creatinine ($p = 0.001$), white blood cell ($p < 0.001$), and neutrophils ($p < 0.001$) were significantly elevated, whereas the estimated glomerular filtration rate ($p = 0.003$) was decreased in the pancreatic injury group. Survival rates did not differ significantly between the two groups.

Conclusion: Elevated pancreatic enzyme levels up to three times the upper limit of normal did not significantly impact all-cause mortality, but were linked to higher rates of inflammatory markers and ICU admission in the first week of hospitalization.

Keywords: COVID-19, pancreatic enzyme elevations, amylase, lipase

INTRODUCTION

The COVID-19 pandemic has impacted people's health, the economy, and societal structure. Understanding the complex nature of this virus, its transmission, and its impacts on different populations is crucial for effective management and prevention strategies. COVID-19 usually presents with respiratory symptoms and, in some cases, can progress to severe pneumonia, leading to acute respiratory distress syndrome (ARDS) (1). The clinical spectrum of coronavirus is broad, encompassing both asymptomatic cases and severe illnesses that require intensive care. Besides respiratory symptoms, gastrointestinal symptoms like nausea, with or without vomiting, have been noted in some patients, although they

are less common (2). The disease has also been connected to various orofacial manifestations, highlighting the diverse clinical presentations that can occur (3). Acute pancreatitis has emerged as a notable complication associated with COVID-19 infection, with various studies emphasizing its potential mechanisms and prevalence among affected patients. COVID-19-related acute pancreatitis may result from direct and indirect effects of the virus on the pancreas. The existence of angiotensin-converting enzyme 2 (ACE2) receptors in pancreatic cells suggests that SARS-CoV-2 can directly infect these cells, leading to inflammation and damage (4-7). The inflammatory response caused by COVID-19, marked by a cytokine storm, can aggravate pancreatic damage through mechanisms like vasculitis

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and microthrombosis (8,9). It is still uncertain whether the rise in pancreatic enzymes is directly related to disease severity or if it indicates a greater risk of death. Our research aims to investigate how elevated pancreatic enzymes relate to the outcomes of COVID-19 patients.

MATERIAL AND METHOD

Ethical approval for this study was granted by the Kütahya Health Sciences University Faculty of Medicine Local Ethics Committee (Decision No. 2023/13-06; Date: 28 November 2023).

Study Design

From January 1 to December 31, 2021, we retrospectively evaluated our study at a tertiary education and research hospital. In our study, we analyzed patient data, such as demographics, medical history, imaging results, laboratory results, treatment plans, and outcomes.

Patient Selection

Data from 457 patients in internal medicine and intensive care unit (ICU) were reviewed. Patients with insufficient data and those without a confirmed COVID-19 diagnosis by PCR testing weren't included in the research. In fulfillment of the inclusion requirements outlined below, the study involved 376 patients (Figure 1).

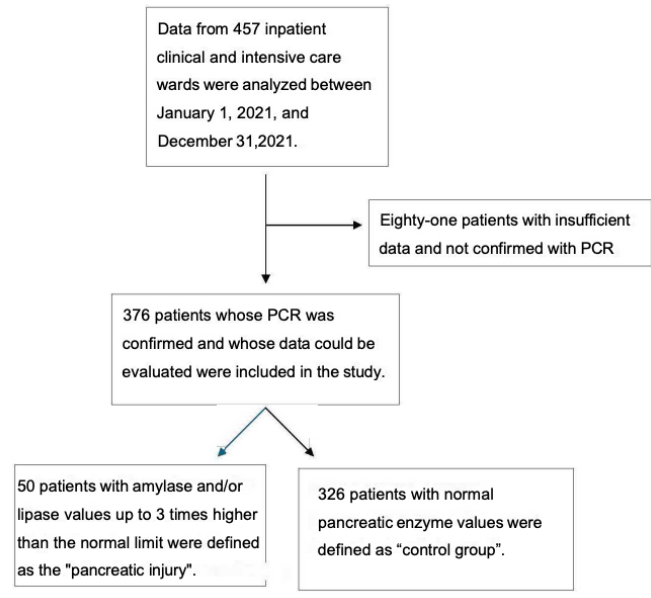


Figure 1. The flowchart illustrating the study design provides an overview of the patient selection process

It was planned to include patients: 1. Whose records were accessed through the automated system, 2. Who were older than 18, 3. Who were not diagnosed with acute pancreatitis for any other reason (e.g., alcohol, gallstones, hyperlipidemia) during their stay in the hospital, 4. Who were monitored in the inpatient intensive care unit and internal medicine wards with a diagnosis of COVID-19 according to the Turkish COVID-19 Adult Patient Treatment Guide of the Ministry of Health (10). A positive PCR result from the patient's nasopharyngeal swab samples was

used to confirm a COVID-19 diagnosis. The patient was admitted to the hospital.

ICU Admission Criteria

Patients meeting intensive care criteria upon admission, such as those with severe respiratory failure, hemodynamic irregularity, change in mental status, multiorgan failure, rapidly progressing radiological findings, elevated inflammatory markers, and persistent clinical deterioration despite optimal medical treatment, were transferred to the ICU for supportive treatment and follow-up. Those not requiring ICU criteria were hospitalized in the clinics; however, patients developing intensive care indications during treatment were transferred to the ICU. The criteria were evaluated according to each patient's condition and determined by the physician.

ICU admission criteria for COVID-19 pneumonia patients included:

- Severe respiratory failure (oxygen saturation [SpO₂] <90% in patients receiving high-flow oxygen therapy or with a rate of respiration greater than 30 breaths per minute),
- Hemodynamic abnormality (need for vasopressors or systolic blood pressure below 90 mmHg),
- Changes in mental state (Glasgow Coma Scale score <13),
- Multiorgan failure (elevated creatinine, aspartate aminotransferase/alanine aminotransferase (AST/ALT), or lactate levels >2 mmol/L),
- Rapidly progressing radiological findings (e.g., bilateral pulmonary infiltrates),
- Elevated inflammatory markers (e.g., White blood cell, D-dimer, C-reactive protein) and persistent clinical deterioration despite optimal medical treatment.

Definition of COVID-19 Severity

COVID-19 severity was categorized based on NIH Guidelines as follows: mild=1, moderate=2, severe=3, and critical=4 (National Institutes of Health [NIH], 2021). The probability of pneumonia was evaluated based on the CO-RADS criteria (11,12).

Data Collection

The medical history, demographic information, clinical findings, laboratory data, and observation results for the patients were gathered using the electronic system. Follow-up and outcome information were also recorded in this manner.

Pancreatic Injury and Pancreatitis Diagnosis

The diagnosis of pancreatitis was made using the 2012 Modified Atlanta criteria, which define The diagnosis of pancreatitis was made using the 2012 Modified Atlanta criteria, which define what constitutes 'pancreatic injury' as amylase and/or lipase levels elevated to three times greater than the normal limit (13). The range of laboratory

levels of serum amylase measured in the local laboratory was accepted as (22-80 U/L), and the lipase value was accepted as (0-67 U/L). Patients with normal pancreatic enzymes were planned to be separated as the control group. Of the 376 patients evaluated, 50 were classified as the 'pancreatic injury group' and 326 as the control group. Clinical, demographic, and laboratory characteristics of the two groups were used to compare them.

Statistical Analysis

All data analyses were performed using SPSS version 27 (IBM®, Chicago, USA). The normality of continuous variables was assessed with the Shapiro-Wilk test and visual inspection of histograms. For continuous variables, data with a normal distribution were summarized using the mean±standard deviation (SD), while data without a normal distribution were summarized using the median (minimum–maximum). The pancreatic injury and control groups were compared using the Chi-square test for categorical variables and the Mann-Whitney U test for nonparametric continuous variables. For the comparison of proportions, the Pearson chi-square test was applied when all expected cell counts exceeded 5, and Fisher’s exact test was used when any expected count was less than 5. To identify independent predictors of ICU admission among patients with pancreatic injury, univariate and multivariate logistic regression analyses were performed. The multivariate model included variables that were

significant in univariate analysis, such as age, creatinine, eGFR (estimated glomerular filtration rate), CRP (C-reactive protein), AST, uric acid, amylase, lipase, white blood cell (WBC) count, D-dimer, and neutrophil count. The results of the logistic regression are presented as odds ratios (OR) with their 95% confidence intervals (CIs). Significance was set at p<0.05 for all analyses.

RESULTS

The study involved 376 participants (50/326). Table 1 presents the demographic data distribution and the clinical parameters of the participants. The mean age was comparable between those with pancreatic injury (M=68.40, SD=15.49) and those without (M=64.94, SD=15.60). Male gender was significantly more prevalent among those with pancreatic injury (X2(1)=4.902, p=0.027). The duration of antibiotherapy (p=0.009), length of hospital stay (p=0.018), and requirement for intensive care at week 1 (p=0.045) were significantly higher in the pancreatic injury group (Figure 2). In terms of disease severity, the control group and the pancreatic injury group were not significantly different; however, the pancreatic injury group had a higher rates of severe disease. Figures 3 and 4 show the correlation between the levels of amylase and lipase and the severity of illness in patients admitted to the intensive care unit within the first fourteen days of illness. Furthermore, there were no variations in all-cause mortality or comorbidity between the groups.

Table 1. Comparison of sociodemographic and clinical characteristics between groups (n=376)				
	All patients (n=376)	Pankreatic injury (+) (n=50)	Pankreatic injury (-) (n=326)	p value
Age, year ¹	65.40±15.64	68.40±15.49	64.94±15.60	0.110
Gender, male ²	201 (53.5)	34 (68)	167 (51.2)	0.027*
Comorbidities (+) ²				
Hypertension	212 (56.5)	32 (64)	180 (55.2)	0.253
Diabetes mellitus	144 (38.4)	16 (32)	128 (39.2)	0.318
COPD	66 (17.6)	8 (16)	58 (17.8)	0.750
Coronary artery disease	62 (16.5)	6 (12)	56 (17.1)	0.354
Congestive heart failure	29 (7.7)	6 (12)	23 (7.1)	0.225
Chronic kidney disease	28 (10.3)	7(14)	21 (6.4)	0.130
Malignancy	46 (12.3)	8(16)	38 (11.6)	0.387
Severity of disease ²				0.157
Mild	112 (29.9)	18 (36)	94 (28.9)	
Moderate	139 (37.1)	12 (24)	127 (39.1)	
Severe	118(31.3)	18 (36)	100 (30.6)	
Critical	7 (1.9)	2 (4)	5 (1.5)	
Duration of antibiotherapy ¹	12.39±7.31	15.20±8.56	11.95±7	0.009*
Length of hospitalization, days ¹	14.72±8.01	17.40±9	14.29±7.78	0.018*
Need for intensive care (first seven days) ²	176 (46.8)	30 (60)	146 (44.8)	0.045*
Mortality ²	109 (30.2)	16 (32)	93 (29.9)	0.764
¹ Mean±sd, Mann Whitney U test; ² n (%), Pearson Chi-square test; COPD: chronic obstructive pulmonary disease; * p<0.05				

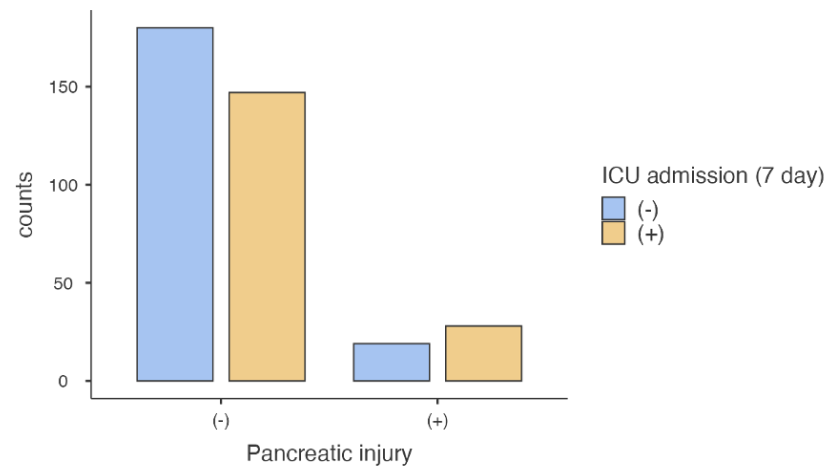


Figure 2. Distribution of ICU admission in the first 7 days between groups with and without pancreatic injury; ICU: Intensive care unit

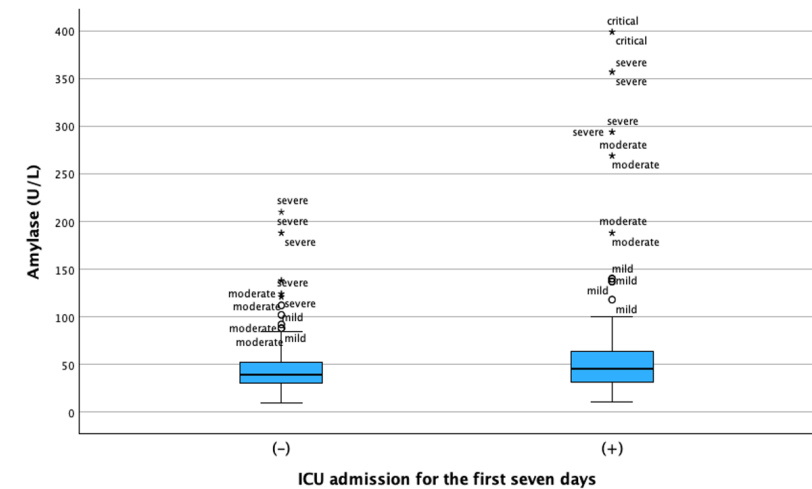


Figure 3. Association between severity of illness and amylase levels in patients admitted to intensive care unit within the first week of hospitalization

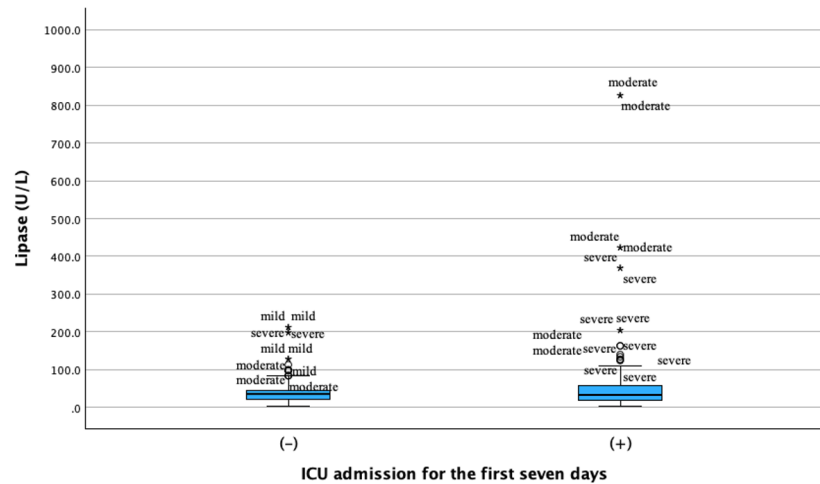


Figure 4. Association between severity of illness and lipase levels in patients admitted to intensive care unit within the first week of hospitalization

The Mann-Whitney U test was employed to evaluate the biochemical values of the groups categorized by pancreatic damage in Table 2. The group with pancreatic injury had considerably greater levels of creatinine ($p=0.001$), white blood cells (WBC) ($p<0.001$), and neutrophils ($p<0.001$), while the group without pancreatic injury had significantly lower levels of estimated glomerular filtration rate (eGFR) ($p=0.003$). There were not significant variations between the groups in uric acid, CRP, D-dimer, or lymphocyte count. Patients without pancreatic damage had significantly higher AST values ($p=0.025$).

Table 2. Comparison of biochemical parameters between groups (n=376)				
	All patients (n=376)	Pankreatic injury (+) (n=50)	Pankreatic injury (-) (n=326)	p value
Creatinine (mg/dL)	1.42±1.27	2.43±2.15	1.27±1.01	0.001*
eGFR (mL/min/1.73m ²)	64.07±31.17	53.84±47.25	65.64±27.68	0.003*
ALT (U/L)	34.44±33.23	35.12±31.29	33.57±33.48	0.061
AST (U/L)	47.82±157.97	45.36±31.19	48.19±169.28	0.025*
Uric acid (mg/dL)	6.27±3.19	6.55±2.51	6.21±3.32	0.185
WBC (x10 ³ /μL)	8914±16497	10730±4051	8631±17651	<0.001*
Neutrophil count (x10 ³ /μL)	6499±4570	9151±3901	6090±4533	<0.001*
Lymphocyte count (x10 ³ /μL)	1900±15164	1118±762	2021±16296	0.845
C- Reactive Protein (mg/L)	92.15±77.69	82.28±64.36	93.68±79.53	0.597
D-dimer (ng/mL)	1487±1319	1654±1118	1461±1348	0.076
Mean±sd, Mann Whitney U test; eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartat aminotransferase, WBC: white blood cell; *p<0.05				

A comparison of the biochemical and clinical features of pancreatic injury patients who were admitted to the ICU and those who were not was conducted using the Mann-Whitney U test along with the Chi-Square Test, as shown in Table 3. Intensive care unit patients had significantly higher WBC (p=0.014), D-dimer (p=0.015), and neutrophil count (p<0.001).

Table 3. Comparison of biochemical and clinical characteristics in patients with pancreatic injury, grouped by the need for intensive care in the first week (n=50)			
	ICU (+) (n=30)	ICU (-) (n=20)	p value
Age, year ¹	71.87±13.88	63.20±16.65	0.095
Gender, male ²	22 (73.3)	12 (60)	0.322
Disease severity ²	21(70)	10 (65)	0.859
Creatinine (mg/dL) ¹	2.97±2.65	1.79±1.09	0.777
eGFR (mL/min/1.73m ²) ¹	53.46±56.17	54.40±30.67	0.234
ALT (U/L) ¹	33.07±21.60	43.20±41.81	0.721
AST (U/L) ¹	43.47±29.21	48.20±34.54	0.552
Uric acid (mg/dL) ¹	6.72±2.32	6.37±2.76	0.189
Amilase (U/L) ¹	173.27±104.18	126.30±40.89	0.191
Lipase (U/L) ¹	175.66±214.15	101.40±60.51	0.634
WBC (x10 ³ /μL) ¹	11982±4002	8852±3419	0.014*
Neutrophil count (x10 ³ /μL) ¹	10659±3917	6889±2619	<0.001*
Lymphocyte count (x10 ³ /μL) ¹	921±575	1413±916	0.113
C-reactive protein (mg/L) ¹	81.40±60.39	83.60±71.50	0.663
D-dimer (ng/mL) ¹	1792±1302	1235±1281	0.015*
¹ Mean±sd, Mann Whitney U test; ² n (%), Chi-square; eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartat aminotransferase, WBC: white blood cell; * p<0.05			

Table 4 represents the results of univariate and multivariate logistic regression analyses evaluating factors associated with the need for intensive care during the first week of hospitalization in patients with pancreatic injury. In the univariate analysis, older age (OR=1.035, 95% CI: 1.021–1.050, p<0.01), elevated creatinine (OR=1.281, 95% CI: 1.056–1.555, p=0.012), lower eGFR (OR=0.993, 95% CI: 0.987–1.000, p=0.046), higher AST (OR=1.009, 95% CI: 1.002–1.016, p=0.015), uric acid (OR=1.098, 95% CI: 1.001–1.204, p=0.048), amylase (OR=1.006, 95% CI: 1.002–1.011, p=0.008), lipase (OR=1.005, 95% CI: 1.001–1.010, p=0.022), neutrophil count (p<0.001), C-reactive protein (OR=1.005, 95% CI: 1.002–1.007, p=0.001), and D-dimer (p<0.001) were significantly associated with the requirement for intensive care during the first week of hospitalization in patients with pancreatic injury. Age (OR=1.044, 95% CI: 1.016–1.074, p=0.002), amylase (OR=0.992, 95% CI: 0.984–0.999, p=0.033), lipase (OR=1.008, 95% CI: 1.001–1.015, p=0.033), and neutrophil count (p=0.018) were independent predictors in the multivariate analysis.

Table 4. Univariate and multivariate logistic regression analysis of patients with pancreatic injury requiring intensive care during the first week of hospitalization (n=50)						
	Univariate			Multivariate		
	OR	CI 95%	p	OR	CI 95%	p
Age, year	1.035	1.021-1.050	<0.01*	1.044	1.016-1.074	0.002*
Gender, male	0.743	0.494-1.116	0.152			
Disease severity	0.986	0.593-1.642	0.958			
Creatinine (mg/dL)	1.281	1.056-1.555	0.012*	1.317	0.934-1.858	0.116
eGFR (mL/min/1.73m ²)	0.993	0.987-1.000	0.046*	1.019	1.001-1.037	0.059
ALT (U/L)	1.002	0.996-1.009	0.452			
AST (U/L)	1.009	1.002-1.016	0.015*	1.001	0.996-1.006	0.674
Uric acid (mg/dL)	1.098	1.001-1.204	0.048*	1.067	0.946-1.204	0.293
Amylase (U/L)	1.006	1.002-1.011	0.008*	0.992	0.984-0.999	0.033*
Lipase (U/L)	1.005	1.001-1.010	0.022*	1.008	1.001-1.015	0.033*
WBC (x10 ³ /μL)	1.000	1.000-1.000	<0.001*	1.000	1.000-1.000	0.659
Neutrophil count (x10 ³ /μL)	1.000	1.000-1.000	<0.001*	1.000	1.000-1.000	0.018*
Lymphocyte count (x10 ³ /μL)	1.000	1.000-1.000	0.505			
C-reactive protein (mg/L)	1.005	1.002-1.007	0.001*	1.003	0.998-1.007	0.234
D-dimer (ng/mL)	1.000	1.000-1.001	<0.001*	1.000	1.000-1.000	0.869
-2 Log likelihood: 247.175, Hosmer and Lemeshow Test: p=0.902						
*p<0.05; eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, WBC: white blood count						

DISCUSSION

Aside from respiratory problems, the COVID-19 pandemic has resulted in significant increases in pancreatic enzymes like lipase and amylase. In our study, the term 'pancreatic injury' was deliberately defined more broadly than acute pancreatitis, encompassing cases with elevated amylase and/or lipase levels up to three times the upper limit of normal, regardless of the presence of clinical or radiological features of pancreatitis. This approach recognizes that such enzyme elevations can occur without meeting the diagnostic criteria for acute pancreatitis and may instead reflect systemic inflammation or other extra-pancreatic processes. These rises are linked to various levels of pancreatic damage, which may manifest as acute pancreatitis or hyperenzymemia without obvious clinical symptoms. The pathophysiology behind these enzyme elevations may have multiple causes, including direct viral effects, systemic inflammatory responses, potential microvascular injury complications, and drug-induced effects (14-16).

ACE-2 receptors in pancreatic tissue are key to understanding COVID-19-associated pancreatic injury. These receptors enable SARS-CoV-2 to enter host cells, and their presence in pancreatic cells can cause direct damage, leading to increased amylase and lipase levels in the blood (14). As evidenced by elevated C-reactive protein and other inflammatory markers like interleukin-6, systemic inflammation exacerbates pancreatic damage (15,16).

According to our findings, patients with elevated pancreatic enzymes had a significantly longer hospital stay, required more antibiotics, and required intensive care during the first

week. Secondary infections in this patient group may be caused by mechanisms such as an intense inflammatory response and immunosuppression. Additionally, prolonged antibiotic use may lead to the colonization of resistant bacteria and decreased antibiotic efficacy. This situation might also lead to an increase the risk of infection exposure in COVID-19 patients, raising treatment costs and creating an added burden on their morbidity.

In epidemiological studies, increased levels of pancreatic enzymes were found to be highly associated with COVID-19 severity. A study with 1,249 patients found that 2.96% showed elevated amylase and lipase levels, with a higher occurrence in severe cases compared to mild infections. (17). Similarly, in our study, 4.3% of patients developed hyperlipasemia, 12.2% developed hyperamylasemia, and 3.2% developed both hyperamylasemia and hyperlipasemia. Research indicates that up to 17% of patients with severe COVID-19 may have abnormal enzyme levels, which are indicative of pancreatic injury. (18,19). We reported 17.5% of pancreatic injuries in moderate, severe, and critical cases. This indicates that monitoring pancreatic enzyme levels could be an important prognostic tool in managing COVID-19 patients.

The elevation of lipase and amylase is not limited to pancreatitis and, in many cases, does not indicate direct pancreatic injury at all. Our study therefore emphasizes that enzyme elevation, as defined in our broader 'pancreatic injury' category, can also serve as a surrogate marker of systemic inflammation in COVID-19 patients. Other conditions, such as renal failure, liver disease, and gastrointestinal disorders, can also cause increased levels of these enzymes (20). It is essential to decide

if the hyperlipasemia and/or hyperamylasemia seen in COVID-19 patients indicates significant pancreatic damage or merely reflects systemic illnesses. Nearly fifty percent of those with elevated levels of lipase did not fit the criteria for acute pancreatitis, according to a study, which suggests that many cases of hyperlipasemia may have non-pancreatic causes (21,22). The severity of the illness and tissue and organ ischemia may both have an important role in the increase in pancreatic enzyme levels. Due to its complexity, diagnosing pancreatitis in COVID-19 requires careful clinical evaluation and imaging tests for confirmation.

The clinical presentation of COVID-19-related pancreatic injury can vary significantly. Some patients may display classic signs of acute pancreatitis, such as abdominal pain and nausea, while others might only show mild increases in pancreatic enzymes without notable clinical symptoms (23,24). In a cohort study, only 7.5% of patients with elevated lipase levels had imaging-confirmed pancreatitis, highlighting the need for a comprehensive diagnostic approach (25,26). The lack of a distinct connection between enzyme levels and clinical symptoms makes managing these patients more difficult because elevated enzyme levels do not always signify acute pancreatitis.

An unexpected finding in our study was that AST levels were significantly higher in the group without pancreatic injury compared to the group with pancreatic injury ($p=0.025$, Table 2). This observation appears to contrast with the general trend in our results, where the pancreatic injury group demonstrated more pronounced systemic inflammation and organ dysfunction markers. One possible explanation is that in the non-pancreatic injury group, AST elevation may have been driven by alternative mechanisms, such as concomitant hepatic injury due to viral hepatitis, drug-induced liver injury, ischemic hepatitis secondary to hypoxia, or muscle injury (given AST's non-specific tissue distribution). Additionally, pre-existing chronic liver disease or other comorbid conditions not evenly distributed between groups could have contributed to this difference.

Despite the fact that the two groups' differences in D-dimer levels were not statistically significant, we found that the group with pancreatic injury tended to have higher D-dimer levels. Our analysis also found that the main reasons for the pancreatic injury group being admitted to the intensive care unit in the first week were higher leukocyte counts and D-dimer levels. This elevation in D-dimer levels among patients with pancreatic injury suggests a potential link to systemic coagulation alterations, which may complicate their clinical course. Since elevated D-dimer levels are indicative of the underlying inflammatory and coagulopathic processes that can occur during critical illness, they have been linked to poor outcomes in acute pancreatitis (27). Furthermore, comorbidities like diabetes mellitus may worsen these complications, increasing the risk of severe pancreatic damage and subsequent ICU admissions. (28). It's crucial for clinicians to grasp these connections, as tracking D-dimer levels can help predict

pancreatic injury severity and guide treatments to improve patient outcomes.

Our study has some weaknesses. The retrospective design complicates causal clarification and limits result generalizability. Also, we can't say for sure that the data are due to SARS-CoV-2 effects because there wasn't a control group to compare the results to people who didn't have COVID-19. However, because the patients' full clinical findings and imaging results were not completely available, verifying the acute pancreatitis diagnosis was difficult. Finally, the insufficient number of patients for subgroup analyses concerning various comorbidities prevents a comprehensive understanding of the clinical course of enzyme elevation in these patients.

CONCLUSION

The complex nature of elevated amylase and lipase in COVID-19 patients necessitates additional research to fully understand its implications. Understanding the connection between direct viral effects, systemic inflammation, and comorbidities makes it challenging to interpret these enzyme levels. Clinicians should monitor pancreatic enzyme levels in COVID-19 patients closely, as they may signal underlying pancreatic damage or systemic illness. Future research should address the underlying processes that cause these enzyme elevations and how they affect patient care outcomes.

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Systemic Inflammatory Indices in Preterm Preeclampsia Versus Term Preeclampsia and Healthy Pregnancies: A Retrospective Case-Control Study

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Abstract

Aim: This study aimed to investigate whether systemic inflammatory indices derived from first-trimester complete blood counts—namely the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV)—differ among women with preterm preeclampsia, term preeclampsia, and healthy pregnancies.

Material and Method: In this retrospective case-control study, 197 pregnant women were evaluated and categorized into three groups: preterm preeclampsia (n=39), term preeclampsia (n=59), and healthy controls (n=99). Demographic, perinatal, and hematological data were retrieved from medical records. Inflammatory indices were calculated from complete blood count parameters obtained during the first trimester. Statistical comparisons across groups were performed using one-way ANOVA or Kruskal-Wallis test, with a significance threshold of $p < 0.05$.

Results: While neutrophil counts and hemoglobin levels were significantly higher in preeclampsia groups compared to controls ($p = 0.001$ and $p < 0.001$, respectively), there were no statistically significant differences among groups in terms of NLR ($p = 0.063$), PLR ($p = 0.750$), SII ($p = 0.100$), SIRI ($p = 0.110$), or PIV ($p = 0.091$). Birth weight, birth length, and Apgar scores were significantly lower in the preterm preeclampsia group ($p < 0.001$ for all), reflecting more severe neonatal outcomes.

Conclusion: Despite differences in neutrophil count and hemoglobin concentration, systemic inflammatory indices derived from first-trimester blood counts did not significantly differentiate preterm preeclampsia from term preeclampsia or healthy pregnancies. These findings suggest limited utility of these indices as standalone diagnostic markers in early pregnancy. Future prospective studies incorporating serial measurements and multimodal predictive models are warranted.

Keywords: First-trimester screening, maternal biomarkers, preeclampsia, preterm preeclampsia, systemic inflammation

INTRODUCTION

Preeclampsia is a complex multisystem hypertensive condition distinct to pregnancy, typically presenting beyond 20 weeks of gestation, and defined by the onset of hypertension accompanied by proteinuria or signs of maternal organ disturbance and uteroplacental insufficiency. Affecting roughly 2–8% of pregnancies globally, it continues to be a major contributor to perinatal and maternal mortality and morbidity (1,2). Among its clinical subtypes, preterm preeclampsia—

which necessitates delivery before full-term gestation is achieved—constitutes a more severe phenotype, often associated with adverse outcomes such as impaired fetal development, premature placental detachment, and subsequent neonatal intensive care unit hospitalization (3,4).

Despite substantial scientific investigations, the development of preeclampsia is still not fully elucidated. Central to its development is deficient trophoblast invasion and defective spiral artery reorganization, leading

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to placental hypoperfusion and the subsequent maternal systemic release of antiangiogenic and proinflammatory mediators (5,6). These events collectively contribute to oxidative stress, endothelial dysfunction, and systemic maternal inflammation—key processes implicated in disease progression and severity (7). Elevated circulating concentrations of proinflammatory cytokines (interleukin-6 and tumor necrosis factor- α) along with neutrophil and monocyte activation, underscore the involvement of immune dysregulation in preeclampsia's immunopathophysiology (8,9).

In light of this inflammatory milieu, inflammatory blood markers measured through conventional complete blood count assessments have garnered attention as potential indicators of systemic immune activation in pregnancy. Among these, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are the most widely studied due to their availability and cost-effectiveness. These ratios indicate the equilibrium between innate immune components (neutrophils, platelets) and adaptive immune cells (lymphocytes), and may be perturbed in inflammatory states such as preeclampsia (10,11).

Expanding on these parameters, composite indices including the Systemic Inflammation Response Index (SIRI), Systemic Immune-Inflammation Index (SII) and Pan-Immune-Inflammation Value (PIV) have been developed to present a more integrative assessment of the immune-inflammatory axis. SII is calculated as (platelet count $\times$ neutrophil count) / lymphocyte count, SIRI as (neutrophil $\times$ monocyte) / lymphocyte count, and PIV as (neutrophil $\times$ monocyte $\times$ platelet) / lymphocyte count (12). These indices have demonstrated clinical utility in predicting disease severity and prognosis across a range of inflammatory and neoplastic conditions, including sepsis, cardiovascular disease, and malignancy (13,14).

In obstetric research, the application of these systemic indices for the early prediction or diagnosis of preeclampsia remains limited and yields inconsistent findings. While some studies have reported elevated SII, SIRI, or PIV levels in women who later developed preeclampsia—particularly during the first trimester—others have found no significant associations (15,16). Importantly, few investigations have specifically addressed their diagnostic potential in preterm preeclampsia, a clinically distinct entity with possibly divergent immunologic underpinnings compared to term disease (17,18). This represents a critical gap in the literature, particularly given the higher burden of morbidity associated with early-onset forms.

Accordingly, the present study aimed to evaluate whether systemic inflammatory indices—namely SII, PIV, NLR, PLR and SIRI—differ significantly among pregnant women with preterm preeclampsia, term preeclampsia, and normotensive healthy pregnancies. We hypothesized that these indices, derived from first-trimester complete blood counts, would be significantly elevated in women

with preeclampsia—particularly in those with the preterm phenotype—reflecting a heightened early inflammatory state. This investigation therefore aims to contribute to the development of accessible and cost-effective early biomarkers that may support individualized risk stratification and timely intervention in high-risk pregnancies.

MATERIAL AND METHOD

Research Design and Setting

This retrospective case-control study was conducted at Tekirdağ Namik Kemal University Medical Faculty Hospital. Medical records were reviewed for pregnant women who received antenatal care and delivered between January 1, 2021, and August 1, 2023. Ethical approval for the study protocol was obtained from the institutional ethics committee Namik Kemal University Faculty of Medicine and all procedures adhered to the principles of the Declaration of Helsinki.

Participant Group

Research cohort consisted of three groups of pregnant women:

- **Group 1:** Patients diagnosed with preterm preeclampsia, defined as preeclampsia requiring delivery before 34 weeks of gestation.
- **Group 2:** Patients with term preeclampsia, defined as preeclampsia diagnosed and delivered at or after 37 weeks.
- **Group 3 (Control):** Healthy pregnant women with no history of hypertensive or systemic disease, who delivered at term without maternal or fetal complications.

Preeclampsia was defined as new-onset hypertension—systolic blood pressure of 140 mmHg or higher, or diastolic pressure of at least 90 mmHg—emerging after 20 weeks of pregnancy, accompanied by either proteinuria (300 mg or more in a 24-hour urine sample) or clinical signs of maternal organ dysfunction.

Maternal age was among the exclusion criteria below 18 years, multiple gestation, pre-existing hypertension or diabetes mellitus, chronic inflammatory or autoimmune disease, and presence of any acute infection at the time of blood sampling.

Data Collection

Demographic and clinical variables incorporating variables such as maternal age, gravidity, and parity, abortion history, birth weight, birth length, and Apgar scores were retrieved from hospital records. Complete blood count (CBC) results from the first trimester of pregnancy were recorded for all participants. Blood samples were processed with an automated hematology analyzer in the hospital laboratory under standard protocols.

The following hematological parameters were collected:

- Neutrophil count ($10^3/\mu\text{L}$)
- Lymphocyte count ($10^3/\mu\text{L}$)
- Monocyte count ($10^3/\mu\text{L}$)
- Platelet count ($10^3/\mu\text{L}$)
- Hemoglobin concentration (g/dL)

Based on these values, calculation of inflammatory indices was performed as described below:

- **Neutrophil-to-Lymphocyte Ratio (NLR):** Neutrophil count / Lymphocyte count
- **Platelet-to-Lymphocyte Ratio (PLR):** Platelet count / Lymphocyte count
- **Systemic Immune-Inflammation Index (SII):** (Platelet $\times$ Neutrophil) / Lymphocyte
- **Systemic Inflammation Response Index (SIRI):** (Neutrophil $\times$ Monocyte) / Lymphocyte
- **Pan-Immune-Inflammation Value (PIV):** (Neutrophil $\times$ Monocyte $\times$ Platelet) / Lymphocyte

All calculations were performed using values from the same laboratory reports to ensure consistency and reliability.

Sample Size

All suitable patients according to the inclusion criteria within the study period were included. A total of 197 participants were analyzed: 39 in the preterm preeclampsia group, 59 in the term preeclampsia group, and 99 in the control group.

Statistical Analysis

The data were evaluated using SPSS software, version 22.0. To assess the normality of continuous data, the Kolmogorov–Smirnov test was applied. Non-normally distributed variables were described using medians, along with their respective minimum and maximum values. Group comparisons among the three study cohorts were conducted using one-way ANOVA for variables with normal distribution, while the Kruskal–Wallis H test was applied for those without normal distribution. Categorical data were analyzed using the Chi-square test when applicable. A p-value below 0.05 was considered indicative of statistical significance. When significant differences were identified among groups, post-hoc pairwise comparisons were conducted.

RESULTS

A total of 197 pregnant women were participated in the study, comprising 39 cases of preterm preeclampsia, 59 cases of term preeclampsia, and 99 healthy pregnant women as controls.

Demographic features and neonatal outcomes of the three groups are presented in Table 1. Median maternal age was similar across groups: 26 years (range: 17–46) in the preterm preeclampsia group, 26 years (19–45) in the term preeclampsia group, and 27 years (18–44) in the control group ($p=0.385$). No significant differences were observed among groups in terms of gravidity ($p=0.221$), parity ($p=0.177$), or number of previous abortions ($p=0.883$).

Table 1. Demographic and neonatal characteristics of the study groups.				
	Preterm preeclampsia (n=39) Median (min-max)	Preeclampsia (n=59) Median (min-max)	Control (n=99) Median (min-max)	p
Age (years)	26 (17-46)	26 (19-45)	27 (18-44)	0.385
Gravida	2 (1-8)	2 (1-6)	2 (1-8)	0.221
Parita	1 (1-7)	1(1-7)	2 (1-7)	0.177
Abortus	0 (0-2)	0 (0-2)	0 (0-3)	0.883
Weight (gram)	1470 (310-2405)	2257 (550-3980)	3143 (2330-4210)	<0.001
Length (cm)	38 (23-48)	46 (28-53)	49 (42-53)	<0.001
Apgar scores at 1st min	6 (1-8)	8 (0-9)	9 (7-10)	<0.001
Apgar scores at 5st min	8 (1-9)	9 (0-10)	9 (7-10)	<0.001

Neonatal birth weight showed statistically significant differences, with median values of 1470 g (310–2405) in the preterm preeclampsia group, 2257 g (550–3980) in the term preeclampsia group, and 3143 g (2330–4210) in the control group ($p<0.001$). Similarly, birth length was significantly lower in the preterm preeclampsia group (38 cm, range: 23–48) compared to the term preeclampsia (46 cm, 28–53) and control groups (49 cm, 42–53) ($p<0.001$). Apgar scores at both the 1st and 5th minutes differed significantly between groups. Median Apgar scores at 1

minute were 6 (range: 1–8), 8 (0–9), and 9 (7–10) in the preterm, term, and control groups, respectively ($p<0.001$). At 5 minutes, the respective medians were 8 (1–9), 9 (0–10), and 9 (7–10) ($p<0.001$).

A comparison of blood parameters and derived inflammatory indices is presented in Table 2. Neutrophil counts differed significantly across groups, with medians of $7.2 \times 10^3/\mu\text{L}$ (1.53–15.0), $7.5 \times 10^3/\mu\text{L}$ (3.3–26.2), and $6.3 \times 10^3/\mu\text{L}$ (1.1–13.5) for preterm preeclampsia, term preeclampsia, and controls, respectively ($p=0.001$).

Table 2. Comparison of hematological parameters and systemic inflammatory indices among groups				
	Preterm preeclampsia (n=39) Median (min-max)	Preeclampsia (n=59) Median (min-max)	Control (n=99) Median (min-max)	P
Neutrophil (10 ³ µL)	7.2 (1.53-15.0)	7.5 (3.3-26.2)	6.3 (1.1 -13.5)	0.001
Lymphocyte (10 ³ µL)	1.6 (0.67-3.4)	1.81 (0.7-3.4)	1.9 (0.3-3.4)	0.458
Monocyte (10 ³ µL)	0.53 (0.18-3.3)	0.58 (0.2-9.3)	0.54 (0.06-6.3)	0.474
Hemoglobin (g/dL)	12.2 (9.4 -14.3)	12.3 (8.4-15.7)	11.2 (7.1 -14.5)	<0.001
Platelet (10 ³ µL)	220 (280-391)	251 (49-578)	236 (35- 431)	0.071
NLR	3.7 (0.94-14.2)	4.1 (1.6-17.6)	3.3 (0.8-17.7)	0.063
PLR	451.3 (42.6-7755.8)	139.1 (24.4-446.5)	135.8 (16.7-703.2)	0.750
SII	804.1 (157.7-4147.5)	1005.1 (204.1-5848.7)	805.8 (96.2-3757.9)	0.100
SIRI	2.22 (0.25-20.8)	2.3 (0.49-49.4)	1.7 (0.16-17.3)	0.110
PIV	451.3 (42.6-7755.9)	599.1 (80.9-17880.4)	445.1 (44.5-5110.7)	0.091
NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, LMR: lymphocyte monocyte ratio, SII: systemic inflammatory index (neutrophilxplatelet/lymphocyte count), SIRI: systemic inflammatory response index (neutrophilxmonocyte/lymphocyte count), PIV: pan-immune inflammation value (neutrophilxplateletxmonocyte/lymphocyte count)				

No statistically significant differences were observed among groups for lymphocyte counts (p=0.458), monocyte counts (p=0.474), or platelet counts (p=0.071). Hemoglobin levels were significantly different across groups: 12.2 g/dL (9.4–14.3) in preterm preeclampsia, 12.3 g/dL (8.4–15.7) in term preeclampsia, and 11.2 g/dL (7.1–14.5) in the control group (p<0.001).

The median NLR was 3.7 (0.94–14.2) in preterm preeclampsia, 4.1 (1.6–17.6) in term preeclampsia, and 3.3 (0.8–17.7) in controls (p=0.063). PLR showed wide variability but no significant difference among groups: 451.3 (42.6–7755.8), 139.1 (24.4–446.5), and 135.8 (16.7–703.2) (p=0.750).

SII was 804.1 (157.7–4147.5) in preterm preeclampsia, 1005.1 (204.1–5848.7) in term preeclampsia, and 805.8 (96.2–3757.9) in controls (p=0.100). SIRI values were 2.22 (0.25–20.8), 2.30 (0.49–49.4), and 1.70 (0.16–17.3) in the respective groups (p=0.110). PIV was 451.3 (42.6–7755.9), 599.1 (80.9–17880.4), and 445.1 (44.5–5110.7) (p=0.091).

DISCUSSION

The aim of this study was to evaluate whether systemic inflammatory indices derived from routine complete blood counts differ significantly among pregnant women with preterm preeclampsia, term preeclampsia, and normotensive healthy pregnancies. The primary objective was to determine whether early hematologic markers—particularly NLR, PLR, SII, SIRI, and PIV—might serve as accessible diagnostic or risk stratification tools, especially for more severe, early-onset forms of preeclampsia. Our findings showed that although neutrophil counts and hemoglobin levels differed significantly between groups, the composite inflammatory indices did not demonstrate

statistically significant intergroup differences. These results suggest limited utility of these markers for distinguishing preterm preeclampsia from either term preeclampsia or healthy pregnancies in a clinical setting.

Our findings regarding elevated neutrophil counts in preeclampsia are consistent with earlier studies, which have demonstrated leukocyte activation and systemic inflammatory responses as central features in preeclamptic pathophysiology (1,5,7). Neutrophils have been shown to contribute to endothelial dysfunction through increased generation of reactive oxygen species, proteases, and inflammatory cytokines (6,8). This proinflammatory profile may explain why neutrophil counts are elevated in both preterm and term preeclampsia, yet it is noteworthy that the derived NLR did not differ significantly. This finding aligns with prior reports that question the sensitivity of NLR as a solitary marker in predicting or diagnosing preeclampsia (10,11).

Similarly, while platelet counts trended lower in preeclampsia—particularly in preterm cases, possibly reflecting platelet activation and consumption—the PLR exhibited high variability and showed no significant differences between groups. Several studies have shown inconsistent associations between PLR and preeclampsia, with some suggesting a potential diagnostic role and others reporting negligible or non-significant differences (10,11,15). These discrepancies may be due to differences in study populations, timing of sample collection, and varying definitions of preeclampsia severity.

More importantly, our study evaluated newer composite indices such as the SII, PIV and SIRI which were hypothesized to provide a broader view of systemic inflammation. Contrary to expectations, none of these indices demonstrated statistically significant differences

between groups. Although the median values of SII and PIV were numerically higher in the term preeclampsia group, the wide ranges and overlapping distributions precluded meaningful discrimination. These findings suggest that the degree of systemic inflammation reflected by these indices may not differ substantially between early- and late-onset preeclampsia, or between preeclamptic and healthy pregnancies, when measured in the first trimester.

Our results partly contrast with a study published recently by Seyhanli et al., which reported significantly elevated first-trimester SIRI and PIV values in women who later developed preeclampsia, suggesting a potential predictive role (15). However, their study combined both preterm and term preeclampsia and focused on predictive rather than diagnostic value. In our study, group comparisons were performed after the diagnosis of preeclampsia, which may explain the lack of observed differences. Furthermore, our sample included only cases with clearly defined preterm and term classifications, allowing for finer subgroup analysis but also potentially reducing statistical power.

Another study by Genç and Erdal found that PIV and SII were elevated in women with early pregnancy losses, suggesting that these indices may reflect a heightened proinflammatory state (16). Their relevance to preeclampsia remains uncertain, as inflammatory patterns in spontaneous abortion and hypertensive disorders of pregnancy may differ significantly. Nevertheless, these findings underscore the need for further exploration of how hematologic indices relate to diverse obstetric outcomes.

While our study did not identify significant diagnostic value for these markers, it is noteworthy that some research in non-obstetric populations—such as oncology and critical illness—has demonstrated strong correlations between systemic inflammatory indices and disease severity or prognosis (13,14). It is possible that in preeclampsia, systemic inflammation occurs on a spectrum and that these indices reflect only part of the complex pathophysiological process. Additionally, the heterogeneity of immune responses among pregnant women, influenced by factors such as parity, age, genetic predisposition, and environmental exposures, may obscure any consistent pattern of hematologic change.

This study has several strengths. It is among the few that directly compare systemic inflammatory indices in preterm versus term preeclampsia, using a well-defined control group and laboratory data obtained in the first trimester. The inclusion of novel indices such as SIRI and PIV adds value to the existing literature, as few studies have examined their role in obstetrics. Furthermore, the use of routine and widely available hematological parameters enhances the potential applicability of the findings in clinical settings.

Nonetheless, several limitations must be acknowledged. The retrospective design limits control over confounding variables, such as undetected subclinical infections or other inflammatory conditions. The study also lacked adjustment for body mass index (BMI), smoking status, and other lifestyle-related inflammatory modifiers. In addition,

inflammatory indices were derived from single time-point measurements, which may not capture dynamic changes throughout pregnancy. Serial measurements could provide deeper insights into the temporal evolution of inflammatory profiles in preeclampsia. Moreover, although first-trimester blood samples were prioritized, it is possible that not all cases had uniform timing of laboratory assessment. Finally, the sample size, while adequate for group-level comparisons, may have been underpowered for detecting small effect sizes, particularly for highly variable indices such as PLR and PIV.

In light of these findings, systemic inflammatory indices derived from complete blood counts should be interpreted with caution in the context of preeclampsia diagnosis or stratification. While they offer a cost-effective and accessible approach to evaluating systemic immune activity, their standalone diagnostic accuracy appears limited. Future research should aim to integrate these indices into multifactorial prediction models incorporating biochemical, angiogenic, and Doppler ultrasound parameters to improve early detection and risk classification of preeclampsia. Prospective studies with larger, diverse cohorts and serial measurements are warranted to validate the predictive potential of these indices, particularly in high-risk pregnancies.

CONCLUSION

This study demonstrates that although neutrophil counts and hemoglobin levels were significantly elevated in women with preeclampsia, systemic inflammatory indices derived from first-trimester complete blood counts—namely SII, NLR, SIRI, PLR and PIV—did not differ significantly among patients with preterm preeclampsia, term preeclampsia, and healthy pregnancies. These findings suggest that such indices, when used in isolation, may have limited diagnostic utility in distinguishing early-onset and late-onset preeclampsia during early gestation. Given their accessibility and cost-effectiveness, these hematologic markers may still hold value when integrated into multifactorial prediction models. Future prospective studies incorporating serial measurements, larger sample sizes, and additional biochemical or imaging parameters are warranted to better elucidate their role in early risk stratification of preeclampsia.

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The Effect of Individual Valproic Acid and Albumin Variation on the Risk of Episodes in Patients with Bipolar Disorder

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Abstract

Aim: This study aimed to investigate the association between the coefficient of variation (CV%) of valproic acid (VPA) and albumin levels and mood episode status in patients with bipolar disorder who maintained therapeutic VPA concentrations.

Material and Method: Patients diagnosed with bipolar disorder who had been under follow-up for at least two years between 2018 and 2023 were retrospectively analyzed. Inclusion criteria required at least three annual measurements of simultaneous serum VPA and albumin levels, with VPA consistently within the therapeutic range (45–100 µg/mL). Patients were categorized based on episode occurrence. Mean values, standard deviation (SD), and CV% were calculated for VPA and albumin levels.

Results: A total of 90 patients with bipolar disorder were included, with 45 experiencing episodes and 45 remaining episode-free. The mean of the last six albumin measurements was significantly lower in the episode group ($t=-2.688$, $p=0.009$). While the CV% of total VPA levels did not differ significantly between groups, the CV% of albumin-adjusted VPA levels was significantly higher in the episode group ($z=-2.005$, $p=0.045$). Episode frequency showed a statistically significant but weak positive correlation with both normalized SD ($r=0.281$, $p=0.007$) and normalized CV% ($r=0.260$, $p=0.013$).

Conclusion: This study found that individuals with bipolar disorder who experienced episodes had significantly lower serum albumin levels, and that albumin-adjusted VPA fluctuations showed a weak but positive correlation with episode occurrence. Prioritizing the CV% of albumin-adjusted VPA measurements may play a significant role in monitoring episode risk in patients with bipolar disorder.

Keywords: Bipolar disorder, valproic acid, coefficient of variation, albumin, mood episode

INTRODUCTION

Bipolar disorder is a chronic psychiatric illness marked by recurrent episodes of depression and either mania or hypomania (1). While bipolar I disorder includes episodes of both depression and full mania, bipolar II disorder is defined by the occurrence of depressive episodes accompanied by hypomanic episodes—milder periods of mood elevation that typically do not lead to marked functional impairment (2). Epidemiological studies indicate that the lifetime prevalence of bipolar disorder is approximately 2.4%, with a 12-month prevalence of around 1.5% (3).

In patients diagnosed with bipolar disorder, regular treatment and follow-up are necessary to reduce the frequency of episodes and to minimize the negative

psychological and social impacts associated with the illness. Since 70% of patients are at risk of relapse within 5 years, continuity of treatment and regular follow-up are of great importance (4,5). Preventing the recurrence of depressive or manic episodes is a major challenge in the long-term management of patients with bipolar disorder. Valproic acid (VPA) is considered a reliable treatment option for individuals with bipolar disorder due to its long-term efficacy in reducing episode recurrence and enhancing overall quality of life (6-9). Due to its narrow therapeutic window, potential for drug-drug interactions and significant variability in pharmacokinetics across individuals, VPA treatment necessitates routine monitoring of serum levels (10). In addition, the absorption and elimination of VPA are affected by its non-linear kinetics

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and variable protein binding, factors that can change notably between different age groups (9). Leading clinical guidelines such as those from the British Association for Psychopharmacology (11), the Canadian Network for Mood and Anxiety Treatments (8), the International Society for Bipolar Disorders, and the National Institute for Health and Care Excellence (12) do not recommend a specific optimal serum VPA range; instead, they emphasize the importance of maintaining serum levels within the generally accepted therapeutic range (e.g., 50–100 µg/mL) (9). The 2013 guideline of the World Federation of Societies of Biological Psychiatry recommended a VPA concentration range of 45–100 µg/mL for patients with bipolar disorder (13).

VPA is transported in the blood with approximately 90% bound to serum proteins, particularly albumin. Research indicates that variations in serum albumin concentrations may influence the proportion of unbound VPA in the bloodstream (9,14). The free drug concentration is the active portion responsible for the drug's therapeutic effect. Due to the technical difficulty of analyzing free drug levels in many laboratories, total VPA levels are commonly measured instead. In cases where free drug levels cannot be analyzed to assess drug efficacy, corrected VPA levels—calculated using total VPA levels in conjunction with serum albumin levels—are considered to be more informative. Although these calculation formulas are utilized in research settings, they have not been routinely implemented in everyday clinical practice (15).

The coefficient of variation (CV) is a statistical metric used to assess the relative variability of a data set, independent of both the measurement unit and the magnitude of the mean. The coefficient is calculated by taking the ratio of the standard deviation (SD) to the mean and then multiplying by 100 to express the result as a percentage. Since CV reflects the dispersion of values relative to the mean, it is unitless and particularly advantageous when comparing variability across data sets with different scales or units. Unlike the SD, the CV enables more meaningful comparisons between groups with distinct magnitudes and measurement units, making it especially useful for classified or heterogeneous data series (16).

There are studies that examine the relationship between patients' serum VPA levels and the risk of experiencing episodes (9,17,18). Although serum VPA levels may remain within the therapeutic range, some patients continue to experience manic and/or depressive episodes, suggesting that treatment response cannot be explained solely by serum concentrations (19). To the best of our knowledge, no existing study has conducted a detailed analysis of variability in serum VPA levels. This study aims to examine the relationship between fluctuations in VPA and albumin levels, and the frequency and risk of mood episodes, in patients diagnosed with bipolar disorder who experience episodes despite maintaining therapeutic VPA serum levels (45–100 µg/mL).

MATERIAL AND METHOD

thical approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Adiyaman University (Approval No: 2023/3-20, dated 14 November 2023), and all procedures adhered to the ethical standards outlined in the Declaration of Helsinki. Bipolar disorder diagnoses were established based on criteria defined in the DSM-5. According to the DSM-5 (20): "A manic episode is characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week and present most of the day, nearly every day. During this period, individuals must exhibit at least three of the following symptoms (or four if the mood is irritable): inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness or pressure to speak, flight of ideas or subjective experience of racing thoughts, distractibility, an increase in goal-directed activity or psychomotor agitation, and excessive involvement in activities with a high potential for painful consequences. A major depressive episode is defined by the presence of five or more symptoms during the same two-week period, with at least one being either depressed mood or a marked loss of interest or pleasure. Other associated symptoms include significant changes in weight or appetite, sleep disturbances (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, indecisiveness, and recurrent thoughts of death or suicidal ideation."

The clinical notes and laboratory results of bipolar disorder patients who presented to the psychiatry clinic of Adiyaman Training and Research Hospital between 2018 and 2023 were retrospectively reviewed in the hospital information system. Patients were included in the study based on the following criteria: absence of organic diseases such as hepatic or renal disorders that could affect serum VPA and albumin levels; a diagnosis of bipolar disorder with regular follow-up over a two-year period; availability of at least three annual measurements of serum VPA and simultaneous albumin levels; and serum VPA levels consistently within the therapeutic range (45–100 µg/mL). Patients were excluded if they had organic conditions (e.g., liver or kidney diseases) that could influence serum VPA concentrations, had fewer than three annual VPA measurements, lacked simultaneous albumin data, or failed to attend regular follow-up visits. Patients were divided into two groups based on their most recent clinical evaluation: those who had serum VPA levels within the therapeutic range and experienced at least one episode within the two-year period, and those with therapeutic serum VPA levels who remained episode-free during the same period.

At the mental health and psychiatry clinic of Adiyaman Training and Research Hospital, VPA levels of bipolar patients in remission are routinely monitored at intervals of 3 to 6 months. To evaluate VPA and albumin levels,

5 cc of venous blood samples were collected from patients 12 hours after the nighttime VPA dose using the antecubital vein. The samples were analyzed using the spectrophotometric method on the Abbott Architect c16000 analyzer (Abbott Diagnostics Inc., Lake Forest, IL, USA), and the results were uploaded to the patient records system within a maximum of 3 days. According to this device, the reference range for VPA is 45–100 µg/mL. The patients' serum VPA levels, normalized according to their albumin values, were calculated using an online calculation tool designed based on the study by Hermida et al. (15).

The study data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows, with a significance level set at $p < 0.05$. For each patient included in the study, the mean, SD, and percent CV% of serum VPA, albumin levels, and albumin-normalized VPA values over a two-year period were calculated. The CV% was computed using the formula: $(SD/mean) \times 100$. The normality of data distribution was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics for quantitative variables were presented as medians along with interquartile ranges (IQRs). For comparisons, the Mann–Whitney U test was applied to non-normally distributed variables, while normally distributed data were analyzed using the Student's t-test. Categorical variables of the groups were compared through the Chi-square test. Associations between variables were explored using Spearman's rank correlation. To determine the diagnostic performance of normalized CV% and SD in predicting episode risk, Receiver Operating Characteristic (ROC) curve analysis was utilized, assessing both sensitivity and specificity.

RESULTS

Between 2018 and 2023, a total of 1563 patients presented to the hospital, and after applying the exclusion criteria, 90 patients were included in the study—45 in the patient group and 45 in the control group. Of the patients included in the study, 32.2% ($n=29$) were female, with a median age of 39 years (33–46). No statistically significant differences were found between the two groups (those who experienced episodes and those who did not) in terms of age and gender ($p=0.944$ and $p=0.259$, respectively). The demographic data of the patients are presented separately for each group in Table 1.

The mean and SD values of the last VPA and albumin results—measured at the most recent visit and over the past two years (six values)—as well as the CV% values calculated using these two parameters, are presented in Table 1. No significant differences were found between bipolar patients with and without episodes in terms of duration of illness, last VPA level, or albumin level.

When the data obtained from the last six VPA values of the patients were compared, no significant differences were found between the groups in terms of mean and CV% values; however, the SD values were found to be significantly higher in the group that experienced episodes ($p=0.048$).

When the data obtained from the last six albumin levels of the patients were compared, the mean value was found to be significantly lower in the episode group [3.80 (3.55–4.11) vs 3.94 (3.78–4.21), $p=0.009$], while no statistically significant differences were observed in SD and CV% values.

Table 1. Demographic data and laboratory results of the patients with bipolar disorder

	Episode group (n=45) (Median)	Non-episode group (n=45) (Median)	P value
Age*	37 (33.5-45.5)	40 (32.5-46)	0.944 (z=-0.008)
Gender, (n%)			
Female	12 (26.7%)	17 (37.8%)	0.259 ($\chi^2=1.272$)
Male	33 (73.3%)	28 (62.2%)	
Duration of illness*	15(10-22.5)	12 (7.5-17.5)	0.082 (t=1.762)
Frequency of manic episodes in the last two years*	2 (2-3)	0	
Frequency of depressive episodes in the last two years*	1 (1-1)	0	
Total episode frequency in the last two years*	3 (2.5-4)	0	
Last VPA level*	79.2 (65.5-89.6)	77.5 (62.5-86.65)	0.487 (t=0.730)
Mean of the last 6 VPA levels*	70.18 (67.78-85.12)	76.11 (68.49-84.12)	0.331 (z=-0.972)
SD of the last 6 VPA levels*	13.25 (9.78-17.17)	9.96 (7.29-15.22)	0.048 (z=-1.973)
CV% of the last 6 VPA levels*	18.26 (13.78-21.34)	14.20 (10.32-19.81)	0.084 (t=1.748)
Last ALB level*	3.90 (3.6-4.25)	4.00 (3.75-4.25)	0.171 (t=-1.381)
Mean of the last 6 ALB levels*	3.80 (3.55-4.11)	3.94 (3.78-4.21)	0.009 (t=-2.688)
SD of the last 6 ALB levels*	0.31 (0.21-0.4)	0.29 (0.19-0.39)	0.534 (z=-0.621)
CV% of the last 6 ALB levels*	7.87 (5.26-10.44)	7.44 (4.86-9.97)	0.345 (z=-0.944)

*The data is presented as median (Interquartile range); CV%: coefficient of variation, SD: standard deviation, VPA: valproic acid, ALB: albumin

The data of VPA values normalized based on the patients' current albumin levels are presented in Table 2. While no significant difference was found between the groups in the adjusted mean values of the last 6 normalized VPA results, the normalized SD and normalized CV% values were significantly higher in the group that experienced

episodes [normalized SD: 23.28 (16.09–37.53) vs 20.09 (12.46–28.01), $p=0.030$; normalized CV%: 23.57 (18.02–36.15) vs 20.26 (15.17–28.68), $p=0.045$]. The lower mean albumin levels in the episode group led to relatively higher calculated normalized VPA values in this group, although the difference was not statistically significant.

Table 2. Valproic acid levels of the patients normalized based on serum albumin			
	Episode group (n=45) (Median)	Non-episode group (n=45) (Median)	P value
Mean of the last 6 normalized VPA levels*	99.26 (84.64-115.08)	93.55 (76.78-105.23)	0.058 (z=-1.896)
SD of the last 6 normalized VPA levels*	23.28 (16.09-37.53)	20.09 (12.46-28.01)	0.030 (z=-2.175)
CV% of the last 6 normalized VPA levels*	23.57(18.02-36.15)	20.26 (15.17-28.68)	0.045 (z=-2.005)
*The data is presented as median (Interquartile range); CV%:coefficient of variation, SD: standard deviation, VPA: valproic acid			

A statistically significant but weak correlation was observed between episode frequency and both normalized SD and normalized CV% ($p=0.007$, $r=0.281$; $p=0.013$, $r=0.260$, respectively). In the ROC analysis performed to assess the predictive value of normalized SD and CV% for mood episodes, the area under the curve (AUC) was 0.633 (95% CI: 0.518–0.748; $p=0.030$) for SD and 0.623 (95% CI: 0.507–0.739; $p=0.045$) for CV%. Based on the Youden index, the optimal cutoff value for CV% in predicting episode occurrence was ≥ 17.55 , yielding a sensitivity of 82% and specificity of 40%. Similarly, the optimal cutoff for SD was ≥ 14.95 , with the same sensitivity (82%) and specificity (40%) (Figure 1).

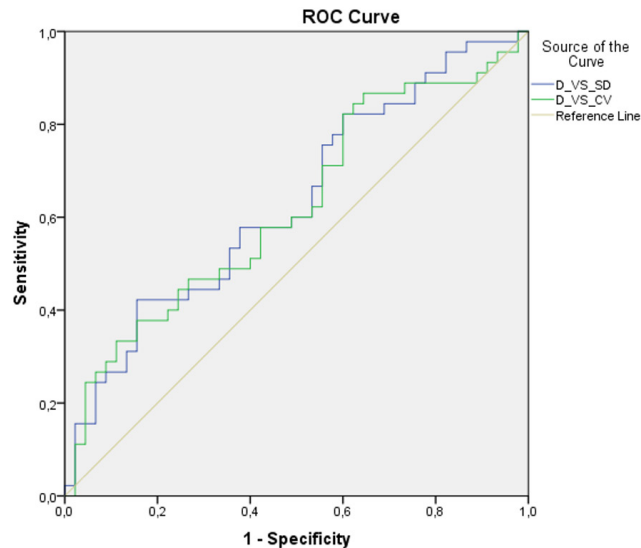


Figure 1. ROC analysis of normalized standard deviation and coefficient of variation in predicting mood episode risk

DISCUSSION

In this study, no statistically significant difference in gender distribution was found between the groups: patients who experienced manic or depressive episodes and those who did not, despite having therapeutic VPA levels. This finding is partially inconsistent with some reports in the literature. For instance, studies by Slyepchenko et al. (21) and Menculini et al. (22) have

reported that rapid cycling episodes are more frequently observed in female patients. However, in our sample, gender did not significantly influence the likelihood of experiencing episodes. This discrepancy may be attributed to methodological differences such as the relatively small sample size, the potential influence of unmeasured biological or environmental factors affecting treatment response, or the fact that our study focused on episode frequency rather than the presence of rapid cycling. In addition, no statistically significant age difference was found between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, it is noteworthy that both groups had a relatively higher mean age (approximately 37–40 years) compared to the general bipolar disorder population. This finding may reflect a greater motivation for regular clinical follow-up among older individuals, potentially due to age-related changes in VPA metabolism that increase the proportion of free drug and, consequently, the risk of toxicity, as reported in previous studies (23,24). Another possible explanation is that clinicians may adopt closer monitoring strategies for older patients in anticipation of age-related pharmacokinetic alterations. In this context, advanced age may not only indicate increased vulnerability to adverse effects but also signal the need for more careful clinical supervision.

In this study, no significant difference has been found in the duration of illness between bipolar disorder patients with therapeutic VPA levels who experienced episodes and those who did not. This finding suggests that the duration of illness alone is not a determining factor for episode frequency. Bukh et al. (25) have reported that the frequency of episodes increases with the progression of illness duration in bipolar disorder. In contrast, Gitlin and Frye (26) have found that, over long-term follow-up, consistent adherence to pharmacological treatment and the presence of individual protective factors are more decisive in determining episode frequency. In our study, since both patient groups had VPA levels within the therapeutic range, the presence of biological treatment adherence may have masked any potential differences in episode risk associated with illness

duration. Nevertheless, it is suggested that the impact of illness duration on episode occurrence may be more strongly linked not solely to the length of the illness, but to accompanying factors such as early onset, psychotic features, comorbid substance use, and affective temperament (27).

In the analysis of the last six albumin levels of the patients, the SD and CV% values did not show a significant difference between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, the mean albumin levels were found to be significantly lower in the episode group, which resulted in relatively higher calculated normalized VPA values in this group. As is well known, VPA is a drug that binds extensively to albumin, and in cases of hypoalbuminemia, the free (active) fraction increases (28). This increase may lead to free VPA levels exceeding therapeutic limits, even when total VPA levels remain within the therapeutic range, potentially enhancing both the drug's effects and the risk of side effects. In the study conducted by Chen et al. (9), it has been reported that individuals diagnosed with bipolar disorder who have serum VPA levels above 75 µg/mL exhibited more variable and statistically non-significant outcomes regarding mood episode recurrence compared to those with levels between 50–74 µg/mL. The researchers explained this by suggesting that a certain threshold level may be exceeded at the protein-binding sites of VPA in the serum. Accordingly, an increase in VPA levels does not always confer a protective effect against mood episodes; in fact, once the binding sites become saturated, the resulting rise in the free VPA fraction may lead to unpredictable effects on therapeutic efficacy. Therefore, in bipolar disorder patients receiving VPA treatment, it is clinically important to monitor not only total serum levels but also albumin levels, and, if possible, to evaluate free VPA levels to guide appropriate dose adjustments.

In this study, analysis of the last six VPA levels in patients revealed no significant difference in the CV% of total VPA levels between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, the CV% of the corrected VPA levels, calculated using serum albumin concentrations, was found to be significantly higher in the episode group. This finding suggests that fluctuations in corrected VPA levels may increase the risk of experiencing episodes. Variability in the levels of a drug like VPA, which has a narrow therapeutic range, may contribute to both pharmacokinetic instability and clinical variability (9,29).

In the ROC analysis conducted to determine the predictive value of SD and CV% for episodes, we observed that the CV% had a sensitivity of 82% and a specificity of 40% in predicting episode risk. These findings suggest that normalized SD and CV% may serve as sensitive but not highly specific indicators for predicting the risk of episodes. In other words, while these parameters may be valuable in minimizing missed episodes, it should be noted that when

used alone as clinical decision-support tools, they may be associated with a high rate of false positives.

This study has several methodological limitations. First, due to its retrospective design, it was not possible to standardize or control for environmental, psychosocial (stress, sleep disturbances), or biological variables that may have played a role in the emergence of bipolar episodes. Second, the use of antipsychotics, lithium, or other mood stabilizers in addition to VPA treatment poses a potential risk of affecting the pharmacokinetic properties and bioavailability of VPA. Such drug interactions may increase interindividual variability in VPA levels. Another limitation of this study is that the VPA doses and dosing intervals were not provided; instead, the mean, SD, and CV% values of the last six VPA levels were reported. Thirdly, due to an insufficient sample size, episode type could not be included in the subgroup analysis. Fourthly, discrepancies between the timing of blood sample collection and the administration of VPA doses—particularly in the outpatient group—may have complicated the interpretation of measured serum VPA levels. Finally, the weak correlation coefficients between episode frequency, and normalized SD and normalized CV may require to reinterpret of hypotheses in longitudinal studies. Therefore, future prospective and controlled studies are recommended to more closely monitor variables such as dose-time consistency and the effects of concomitant treatments.

CONCLUSION

In conclusion, this study revealed that individuals with bipolar disorder who experienced episodes had significantly lower serum albumin levels compared to those who did not, and that fluctuations over time in VPA levels corrected for serum albumin showed a weak but positive correlation with episode occurrence. These findings suggest that in clinical settings where free VPA levels cannot be directly measured, focusing not only on total VPA levels but also on albumin-corrected VPA values may provide more guidance in patient management. Especially in outpatient follow-up, monitoring the CV% of corrected VPA levels may serve as a supportive parameter for assessing clinical stability and predicting the risk of episodes. In light of these results, future studies with larger sample sizes, prospective designs, and multivariate analyses are warranted.

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Decoding Lung Cancer Mutations: A 5-year Investigation in Ordu Province

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Abstract

Aim: Lung cancer is the leading cause of cancer-related mortality worldwide and is most often diagnosed at an advanced stage. The increasing prominence of targeted therapy approaches in recent years has made the identification of genetic variations within tumors clinically significant. This study aimed to determine the prevalence of key mutations such as EGFR, ALK, KRAS, and PDL-1 in lung cancer cases over a five-year period, along with their distribution across histological subtypes and their association with demographic characteristics, specifically within the province of Ordu.

Material and Method: This retrospective, cross-sectional study included a total of 202 patients who were diagnosed with Non-small cell lung cancer (NSCLC) and presented to the Medical Oncology Clinic of Ordu State Hospital between January 2019 and December 2023. Demographic data such as age and sex, histological subtypes, and genetic mutation analyses and other clinical parameters were evaluated. Mutation analysis focused on actionable biomarkers including EGFR, ALK, KRAS, and PDL-1, and their relationships with demographic characteristics were assessed.

Results: The median age was 67 years (91.1% male). The most frequently observed histological subtype was squamous cell carcinoma (49.5%). In female patients, adenocarcinoma was the predominant (83.3%). The most commonly detected genetic alteration was PDL-1 (10.4%). EGFR mutations were significantly more frequent in older patients, whereas ALK mutations occurred in significantly younger patients.

Conclusion: This study represents the first large-scale lung cancer mutation screening conducted specifically in the Ordu province. Our findings indicate regional differences, with PD-L1 being the most common alteration and squamous cell carcinoma the predominant subtype, in contrast to national data where EGFR mutations and adenocarcinoma are more frequent. These discrepancies indicate that regional characteristics and the genetic profile of the patient population should be taken into consideration during treatment planning.

Keywords: Lung cancer, Ordu province, genetic analysis, mutation

INTRODUCTION

Lung cancer is most often diagnosed at an advanced stage, making its treatment more challenging. In these stages, where the possibility of surgical intervention is generally lost, the response to chemotherapy may be limited. Therefore, the identification of genetic mutations and the development of targeted therapeutic approaches have become increasingly important (1).

According to the most recent national cancer statistics updated in 2020, lung cancer is the most common cancer type among men in Türkiye, accounting for 51.9%, while it ranks fourth among women with a rate of 10.2% (2). Globally, according to the latest GLOBOCAN data

from 2022, lung cancer is the leading cancer type among men and ranks second among women, following breast cancer (3). According to national data, adenocarcinoma is the most frequently observed histological subtype of lung cancer (39%), followed by squamous cell carcinoma (29.6%) (2). In recent years, the emergence of novel treatment modalities in lung cancer has offered hope by contributing to improved survival outcomes. Particularly, the identification of genetic mutations and the development of targeted therapies have increased awareness and transformed treatment strategies. Several scientific studies conducted in Türkiye have also reported the distribution and clinical relevance of mutation analyses in lung cancer (4).

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In the latest version of the National Comprehensive Cancer Network (NCCN) Guidelines updated in June 2025, for patients with advanced or metastatic non-small cell lung cancer (NSCLC), if the histological subtype is adenocarcinoma, large cell carcinoma, or not otherwise specified (NOS), testing for Epidermal growth factor receptor (EGFR), anaplastic lymphoma receptor tyrosine kinase (ALK), kirsten rat sarcoma virus (KRAS), proto-oncogene tyrosine-protein kinase (ROS1), BRAF, neurotrophic tyrosine receptor kinase (NTRK 1/2/3), MET exon 14 skipping, RET, ERBB2 (HER2), neuregulin 1 (NRG1), HER2 (via immunohistochemistry- IHC), and programmed death ligand 1 (PD-L1) is recommended.

Similarly, for patients with advanced or metastatic squamous cell carcinoma, the guidelines recommend testing for EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET, ERBB2 (HER2), NRG1, HER2 (IHC), and PD-L1 (1). The prevalence of mutations varies across different geographic regions. In a study including early-stage (stage IA–IIIB) lung cancer cases from Asia, Latin America, the Middle East, and Africa, the overall EGFR mutation rate was reported as 51%, with a higher prevalence observed particularly among non-smoking women with early-stage disease (5). EGFR mutation rates are generally highest in Asia, reaching up to 49% (6), whereas the prevalence is approximately 17% in the Middle East and North Africa, and the lowest rates have been reported in Europe (14%) (7). It is noteworthy that most of these studies were conducted in patient populations with advanced-stage disease.

Türkiye is considered one of the high-risk countries in terms of genetic disorders. The main contributing factors include the high prevalence of consanguineous marriages, regional isolation, geographic variation in genetic diversity, and historically limited access to screening and diagnostic services (8). Consequently, the prevalence of genetic mutations in lung cancer may be higher in certain regions of Türkiye (4).

Our study was conducted in Ordu, a province located in the northern part of the country, within the Black Sea region—one of Türkiye's seven geographical regions. Due to the mountainous geography of the Black Sea region, certain rural areas have preserved relatively isolated and close-knit populations, which may have contributed to the conservation of specific genetic variants across generations. The rate of consanguineous marriage in this region is close to the national average (approximately 20%). Given its unique population structure and geographic characteristics, the Black Sea region should not be overlooked in terms of genetic disease risk and warrants detailed genetic investigation.

Therefore, in our study, we aimed to investigate—for the first time in the literature—the prevalence of lung cancer-related genetic mutations specifically in the Black Sea region, along with the potential factors influencing these rates.

MATERIAL AND METHOD

Study Design and Patient Selection

This retrospective cross-sectional study was performed at the Medical Oncology Clinic of Ordu State Hospital. The clinical, pathological, and molecular data of patients diagnosed with lung cancer between January 2019 and December 2023 were intended to be explored. Ethical approval was obtained from the Ordu University Noninterventional Scientific Researches Ethics Committee (Date: 22.12.2023, Decision no: 26/330). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients who were eighteen years and above diagnosed with lung cancer within the defined period. Patients whose information could be accessed through the system or medical records were included in the study.

Exclusion criteria: Patients who were less than 18 years old and patients with inconclusive lung cancer diagnoses. Patients whose information could not be accessed through the system or medical records were excluded from the study.

Data Collection and Evaluated Parameters

Medical records of all patients who presented to the outpatient clinic within the specified dates and met the inclusion criteria were reviewed. Of the total 235 patients, 33 were diagnosed with small cell lung cancer and were excluded from the study since mutation analyses were not performed for this subtype. Demographic data, year of diagnosis, histological subtype of lung cancer, disease stage at diagnosis, localization of the primary tumor, diagnostic method, whether genetic mutation analysis was performed, type of mutation (if present), presence of metastasis, and sites of metastasis were recorded from patient files and the hospital's electronic medical record system.

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0. Descriptive characteristics of lung cancer patients were presented as frequencies (n) and percentages (%). Age was summarized using mean, standard deviation, median, minimum, and maximum values. The normality of the age distribution was assessed based on skewness and kurtosis values. A reference range of ± 1.96 was accepted as indicative of normal distribution.

To compare the clinical and diagnostic characteristics of lung cancer patients by histological subtype and gender, the Chi-Square (χ^2) test was used. One-Way Analysis of Variance (ANOVA) was applied to compare patients' ages across different clinical and diagnostic groups. In cases where a statistically significant difference in age was

found among groups, post-hoc tests were performed to determine which groups differed, and group differences were indicated using letter coding.

In all analyses, p-values <0.05 and <0.01 were considered statistically significant.

RESULTS

When molecular testing were evaluated, it was found that no genetic testing had been performed in 57.4% of the cases, while 21.8% were mutation negative. Among the molecular testing, PD-L1 expression was the most frequently observed (10.4%), followed by EGFR (4.0%) and KRAS (3.0%). When comparing adenocarcinoma and squamous cell carcinoma subtypes, a broader spectrum of molecular testing was observed in patients with adenocarcinoma. Specifically, EGFR mutation (7.6%), PD-L1 expression (17.4%), and KRAS (6.5%) mutation were identified in adenocarcinoma cases, whereas these molecular tests were less frequently detected in squamous cell carcinoma. However, the overall distribution of molecular tests between subtypes was not statistically significant ($p>0.05$).

Patients with ALK mutations had a notably lower mean age (39 years), indicating that this mutation is more prominent in younger individuals ($p<0.05$). In female patients, EGFR (16.7%) and ALK (11.1%) mutations were observed more frequently compared to male patients (2.7% and 0.0%, respectively) ($p<0.01$).

The majority of patients were male (91.1%, $n=184$), with a mean age of 66.17 ± 9.06 years, ranging from 38 to 90 years, and a median age of 67. Regarding lung cancer subtypes, the most common histological type was squamous cell carcinoma (49.5%), followed by adenocarcinoma (45.5%) (Figure 1). At the time of diagnosis, 47.5% of patients were in stage IV, indicating that most cases were diagnosed at an advanced stage. Stage III patients accounted for 30.7%, while stage I and II patients represented 11.9% and 9.9%, respectively.

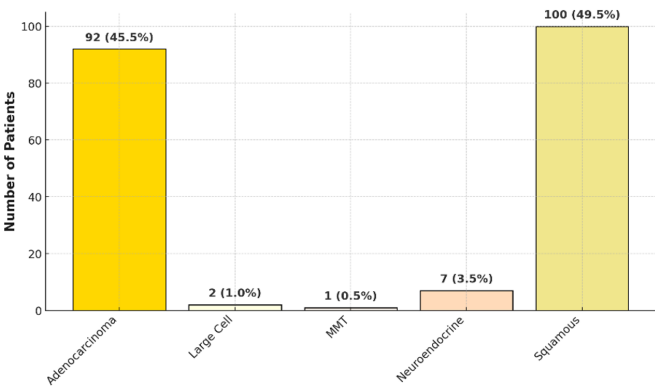


Figure 1. Distribution of lung cancer subtypes

In terms of metastasis, 53% of patients had no detectable metastases. Among those with metastatic disease, the bone was the most common site (16.3%), followed by brain (10.9%), contralateral lung (6.9%), and liver (4.5%) (Table 1).

Table 1. Demographic, clinical, and diagnostic characteristics of NSCLC patients (n=202)		
Variables	Number	%
Gender		
Female	18	8.9
Male	184	91.1
Lung cancer subtype		
Adenocarcinoma	92	45.5
Large cell lung cancer	2	1.0
MMT	1	0.5
Neuroendocrine tumor	7	3.5
Squamous cell carcinoma	100	49.5
Stage		
Stage 1	24	11.9
Stage 2	20	9.9
Stage 3	62	30.7
Stage 4	96	47.5
Metastases		
Bone	33	16.3
Brain	22	10.9
Cervical lymph node	1	0.5
Kidney	2	1.0
Liver	9	4.5
Opposite lung	14	6.9
Pleura	6	3.0
Surrenal	8	4.0
None	107	53.0
Molecular testing		
Not examined	116	57.4
Negative	44	21.8
KRAS	6	3.0
PD-L1	21	10.4
EGFR	8	4.0
ALK	2	1.0
ROS1	1	0.5
HER2	1	0.5
PIK3CA	1	0.5
RET	1	0.5
BRAF	1	0.5
Age		
Mean±SD; Median (Min–Max)		66.17±9.06 67 (38-90)

Regarding treatment, 53.5% of the patients received radiotherapy, 3.0% received targeted therapy, and 11.9% received immunotherapy. The most common sites of primary tumor localization were the right upper lobe (33.2%) and the left upper lobe (26.2%). In terms of diagnostic methods, image-guided transthoracic lung biopsy (40.6%) and bronchoscopic biopsy (37.1%) were the most frequently utilized techniques. When examining the distribution by year of diagnosis, the highest number of cases were diagnosed in 2023 (27.2%).

When demographic, clinical, and diagnostic characteristics were analyzed by gender (Table 2), adenocarcinoma was the most common histological subtype in female patients (83.3%), while the corresponding rate in male

patients was 41.8% (p=0.013). Conversely, squamous cell carcinoma was more prevalent in males (53.3%), whereas this subtype was observed in only 11.1% of female patients. These findings suggest that different histopathological patterns predominate between males and females (p<0.05).

Table 2. Distribution of clinical and diagnostic characteristics of lung cancer patients by gender					
Variables	Female (n=18)		Male (n=184)		p
	Number	%	Number	%	
Lung cancer subtype					
Adenocarcinoma	15	83.3	77	41.8	0.013*
Large cell lung cancer	0	0.0	2	1.1	
MMT	0	0.0	1	0.5	
Neuroendocrine tumor	1	5.6	6	3.3	
Squamous cell carcinoma	2	11.1	98	53.3	
Stage					
Stage 1	4	22.2	20	10.9	0.450
Stage 2	1	5.6	19	10.3	
Stage 3	4	22.2	58	31.5	
Stage 4	9	50.0	87	47.3	
Metastases					
Bone	2	11.1	31	16.8	0.014*
Brain	1	5.6	21	11.4	
Cervical lymph node	1	5.6	0	0.0	
Kidney	0	0.0	2	1.1	
Liver	3	16.7	6	3.3	
Opposite lung	1	5.6	13	7.1	
Pleura	1	5.6	5	2.7	
Surrenal	0	0.0	8	4.3	
None	9	50.0	98	53.3	
Molecular testing					
Not examined	8	44.4	108	58.7	0.000**
Negative	2	11.1	42	22.8	
KRAS	0	0.0	6	3.3	
PD-L1	3	16.7	18	9.8	
EGFR	3	16.7	5	2.7	
ALK	2	11.1	0	0.0	
ROS1	0	0.0	1	0.5	
HER2	0	0.0	1	0.5	
PIK3CA	0	0.0	1	0.5	
RET	0	0.0	1	0.5	
BRAF	0	0.0	1	0.5	
*p<0.05; **p<0.01, Test statistic: Chi-Square Test					

A statistically significant difference was observed between genders regarding metastatic spread (p<0.05). Notably, liver metastasis was detected in 16.7% of female patients compared to 3.3% of male patients (p<0.05). However, no statistically significant differences were found between genders for other variables including disease stage, radiotherapy, targeted therapy, immunotherapy, primary tumor localization, and diagnostic method (p>0.05). The distribution of disease stages was similar between male and female patients, with a high proportion of advanced-stage diagnoses in both groups.

When comparing tumor subtypes, the majority of cases were diagnosed at stage IV, though no statistically

significant difference was found between subtypes (p>0.05). Metastatic patterns varied according to tumor subtype. Liver metastasis was most frequently observed in neuroendocrine tumors (28.6%), while adrenal and bone metastases were more common in squamous cell carcinoma and adenocarcinoma cases. However, these differences did not reach statistical significance (p>0.05).

Regarding primary tumor localization, the right upper lobe was the most frequently involved site in both adenocarcinoma (33.7%) and squamous cell carcinoma (31.0%) cases. However, no statistically significant difference was observed in tumor localization between subtypes (p>0.05). When diagnostic methods were

evaluated, image-guided needle biopsy was the most commonly used technique, with the highest usage rate observed in patients with squamous cell carcinoma (33.0%). Differences among diagnostic methods were not statistically significant ($p>0.05$). Comparison of clinical and diagnostic characteristics according to age revealed that patients with brain metastases were diagnosed at a younger mean age (61.8 years), whereas those with liver metastases were diagnosed at an older mean age (71.8 years) ($p<0.05$).

DISCUSSION

Lung cancer is a malignancy in which early-stage diagnosis allows for significant survival benefits through surgical intervention, whereas in advanced stages, the opportunity for surgery is generally lost, necessitating systemic therapies. Similar to global trends, lung cancer is frequently diagnosed at advanced stages in Türkiye (9). In our study, the majority of patients were diagnosed at stage III (30.7%) and stage IV (47.5%).

In NSCLC, clinical improvements have been observed not only with platinum-based chemotherapy but also through the discovery of genetic molecular tests and the development of mutation-targeted therapies. Several studies have demonstrated that the clinical benefit derived from targeted therapies exceeds that of conventional chemotherapy (10). Furthermore, molecular test-negative NSCLC patients respond better to conventional chemotherapy compared to tyrosine kinase inhibitors (TKIs) directed against EGFR mutations. This underscores the importance of considering molecular results status in treatment selection and adopting a multidisciplinary approach (11).

In Türkiye, it is recommended that molecular testing for EGFR, ALK, and ROS1 genes be performed at the time of diagnosis in all patients with advanced or metastatic (stage IIIB and IV) non-squamous NSCLC. For early-stage patients who have not undergone prior molecular testing, molecular analyses should be conducted upon recurrence or progression, preferably using new biopsy specimens when possible (12).

When examining the frequency of EGFR mutations, the highest rates are observed in Asian countries, while European countries report the lowest frequencies (13). According to the Molecular Testing Guidelines for NSCLC published in 2021 by the Federation of Pathology Societies, EGFR mutation rates are reported to be between 10% and 15%. In our study, however, the EGFR mutation rate was found to be lower, at 4%. Consistent with the literature, EGFR mutations were more frequently detected in female patients in our cohort as well (14).

KRAS mutations represent one of the most common oncogenic alterations in NSCLC worldwide, with prevalence varying by geographic region, ethnicity, and histological subtype (15). The reported prevalence ranges from 8% to 20% in the United States, 9% to 19%

in Europe, 7% to 9% in Latin America, and 1.5% to 4% in Asia (16,17). KRAS mutations occur in approximately 37% of adenocarcinomas but are much less frequent in squamous cell carcinoma (~4.4%). In our study, the KRAS mutation frequency was 3%, aligning more closely with rates reported in Asian populations. Additionally, KRAS positivity was higher in adenocarcinoma cases (6.5%) compared to squamous cell carcinoma (0%) in our cohort.

In recent years, the development of immune checkpoint inhibitors (ICIs) has significantly improved lung cancer prognosis. These inhibitors target the programmed cell death receptor-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, activating anti-tumor immunity and facilitating the elimination of cancer cells (18). Selection of immunotherapeutic agents can be guided by PD-L1 expression status.

In our patient group, PD-L1 expression exhibited the highest frequency at 10.4%. Previous studies report PD-L1 expression prevalence in NSCLC patients ranging from 24% to 60%, even when using a positivity cutoff of 5% (19). To our knowledge, there are no prior studies from Türkiye specifically reporting the frequency of PD-L1 expression.

Adenocarcinoma patients exhibited a broader mutation spectrum, with positivity rates of EGFR (7.6%), KRAS (6.5%) and PD-L1 expression (17.4%) observed in our study. In contrast, mutations and analysis were less frequently detected in squamous cell carcinoma cases. However, no statistically significant difference was found in the overall mutation distribution between these histological subtypes ($p>0.05$). This finding is consistent with previously published literature (20).

One of unexpected finding of a higher frequency of PD-L1 expression compared to EGFR mutations in our cohort, contrary to most national data, may reflect a true regional variation. Several factors could contribute to this discrepancy. The Black Sea region is known for its relatively high smoking rates, and chronic exposure to tobacco smoke is a well-documented inducer of PD-L1 expression in lung tissues. In addition, environmental factors such as air pollution from biomass burning and industrial activity may also play a role in modulating tumor immune markers. Another possible explanation lies in the genetic and ethnic background of the regional population, which may influence tumor biology and immune checkpoint expression patterns. Further studies investigating these environmental and genetic influences are warranted to clarify the underlying mechanisms behind the observed PD-L1 predominance in this region.

Reviewing the literature, our study represents one of the largest single-center analyses to date. Given the regional differences observed, a prospective multicenter study in the Black Sea region appears both necessary and feasible to further elucidate these findings.

Study Limitations

The main limitation of our study is its single-center design. More comprehensive data reflecting the entire Black Sea region could be obtained through multicenter studies involving multiple institutions across the region. Due to the retrospective nature of the study, not all data were accessible from the system, and patients with incomplete records were excluded from the analysis, which may have led to a selection bias in the study population.

CONCLUSION

This study is the first in the Ordu province to provide such comprehensive information about lung cancer. In this study, it was observed that in correlation with research conducted in Türkiye, the majority of patients were diagnosed at advanced stages. This may be attributed to factors such as the non-specific nature of lung cancer symptoms, the late onset of these symptoms, patients attributing the symptoms to smoking, delayed medical consultations, and the absence of a national lung cancer screening program. Developing and implementing lung cancer screening programs, raising public awareness about the harms of smoking and lung cancer, enforcing measures against tobacco and tobacco products, and intensifying smoking cessation programs are necessary to minimize the occurrence and diagnosis of lung cancer in Türkiye.

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Conflict of interest: The authors have no conflicts of interest to declare.

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Quantitative Evaluation of the Parietal Lobes Abnormalities in Sudanese Patients with Schizophrenia: A Comparative Brain Segmentation Study

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Abstract

Aim: Schizophrenia is a long-standing psychiatric condition marked by a gradual deterioration in cognitive functioning, personality organization, and affective responsiveness. This study represents the first magnetic resonance imaging (MRI) investigation to explore morphological similarities and differences of the parietal lobes in Sudanese individuals diagnosed with schizophrenia.

Material and Method: The study cohort comprised 54 patients and 82 healthy participants who met the inclusion criteria. All participants underwent a structured socio demographic assessment and comprehensive physical examination. Brain MRI scans were acquired and subsequently analyzed using automated brain segmentation software applied to DICOM format images.

Results: The mean volume of the parietal lobe was significantly lower in patients ($114.97 \pm 10.86 \text{ cm}^3$) compared to controls ($127.85 \pm 10.65 \text{ cm}^3$). Similarly, volume reductions were seen in both gray and white matter compartments in patients ($72.49 \pm 7.54 \text{ cm}^3$ and $42.47 \pm 4.51 \text{ cm}^3$) compared to controls ($79.40 \pm 6.77 \text{ cm}^3$ and $48.46 \pm 5.94 \text{ cm}^3$). However, no significant difference was observed in the cortical pial surface area of the parietal lobe between groups. Parietal cortical thickness was notably diminished in patients ($p \leq 0.05$).

Conclusion: The reductions observed in total parietal lobe volume, along with diminished gray and white matter volumes in individuals with schizophrenia, indicate a widespread atrophic process affecting this cerebral region. These structural abnormalities may underlie specific cognitive deficits commonly associated with schizophrenia.

Keywords: Parietal lobe; chronic schizophrenia, magnetic resonance images, automatic brain segmentations

INTRODUCTION

Schizophrenia, a chronic and heterogeneous mental illness, manifests through a range of symptoms, including perceptual disturbances, distorted beliefs, disorganized thinking, and cognitive impairments (1). It affects nearly 1% of the global population and is frequently associated with significant impairments in both social interaction and occupational functioning (2). Although its exact etiology remains unclear, compelling evidence suggests that underlying neurodevelopmental disturbances begin during the prenatal phase and extend into adolescence (3,4).

Diagnosis is based on comprehensive history-taking, physical and mental status examinations, and supportive laboratory tests. In addition to clinical rating scales, researchers are actively investigating neuroimaging biomarkers to improve diagnosis, prognosis, and treatment stratification (5).

Brain volumetric assessments using magnetic resonance imaging (MRI) have proven to be effective tools for monitoring the progression of neurodegenerative diseases and evaluating responses to therapeutic interventions. Observing brain volumetric changes in

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schizophrenia can aid in establishing the diagnosis and guiding treatment decisions (6). Neuroimaging research has consistently revealed structural brain alterations in individuals with schizophrenia, encompassing not only those experiencing their first episode or in the prodromal phase but also individuals with a genetic vulnerability to the disorder (7). Gray matter volume and cortical thickness are among the most frequently examined neuroanatomical parameters, both showing widespread alterations, particularly in the frontal, temporal, and parietal lobes (8). Advanced neuroimaging modalities, such as CT and MRI, have highlighted notable structural alterations in individuals with schizophrenia, including an approximate 3% reduction in overall brain volume. This reduction appears to be more pronounced in gray matter (2%) than in white matter (1%) and is often accompanied by enlargement of cerebrospinal fluid compartments, particularly the lateral and third ventricles (9). Consistent decreases in gray matter volume have been documented in several key brain regions, including the anterior cingulate cortex, frontal lobe, superior temporal gyrus, hippocampal–amygdala complex, and the left medial temporal lobe (10,11). These anatomical abnormalities are strongly associated with corresponding functional disturbances (12).

Although numerous studies have investigated various brain regions in schizophrenia, the parietal lobe has received comparatively less attention. Existing evidence indicates structural changes particularly affecting the inferior parietal lobule and its subcomponents, the angular and supramarginal gyri (13,14). These areas are critically involved in language comprehension (15), spatial working memory (16), and attentional processes, all of which are frequently impaired in patients with schizophrenia.

Impairments in cognitive functioning, particularly in domains related to social cognition, are prevalent in schizophrenia and have been associated with morphological changes in key brain regions, including the amygdala, prefrontal cortex, and the temporal and parietal lobes. These alterations frequently involve reductions in both gray and white matter volumes (17). The fronto-parietal network (FPN), comprising interconnected regions within the prefrontal and parietal cortices, plays a critical role in modulating attentional processes (18). Disruptions in white matter integrity within the FPN have been linked to deficits in sustained attention in individuals with schizophrenia (19).

Accordingly, the present study aims to evaluate the total brain volume, as well as gray and white matter volumes, cortical pial surface area, and cortical thickness of the parietal lobes in individuals with schizophrenia. MRI and BrainSuite software were employed for automated brain segmentation and regional parcellation, with particular attention to hemispheric laterality and sex-related differences.

MATERIAL AND METHOD

Subjects

The present hospital-based case-control study employed a cross-sectional design and was conducted in Sudan at Professor Abdelaal Alidresi and Tigani Almahi Psychiatric Hospitals, as well as in several private psychiatric facilities. The sample included 136 participants: 82 healthy controls (47 males, 35 females) and 54 patients diagnosed with schizophrenia (28 males, 26 females). Patients were selected as a convenience sample during the study period, while controls were healthy volunteers with no history of psychiatric illness or psychotropic medication use (Table 1).

Table 1. Comparison of mean age and body mass index (BMI) values between groups			
	n (%)	Age (Years±SD)	BMI (kg/m²±SD)
Male			
Control	47 (34.56)	28.98±5.90	24.65±4.03
Schizophrenic	28 (20.59)	31.11±6.14	22.75±3.39
Female			
Control	35 (25.73)	29.69±6.27	25.51±4.85
Schizophrenic	26 (19.12)	31.69±6.24	24.88±6.06
Total			
Control	82 (60.30)	29.28±6.03	25.02±4.39
Schizophrenic	54 (39.70)	31.39±6.40	23.77±4.93

All participants underwent a semi-structured psychiatric interview, standard mental state examination, physical assessment, and relevant investigations. Diagnoses were made by psychiatric specialists based on the International Classification of Diseases, 10th Revision (ICD-10), as defined by the World Health Organization

(WHO). Patients were on regular antipsychotic treatment, including:

1. Typical antipsychotics (Haloperidol, 2–20 mg/day),
2. Atypical antipsychotics (Olanzapine, 5–20 mg/day) (Table 2).

Table 2. Duration of illness, duration of treatment, and types of treatment in patients with schizophrenia			
	Sex n (%)		Total
	Male	Female	
Duration of the illness			
1-2 years	0 (0.00%)	2 (7.69%)	2 (3.70%)
2-3 years	5 (17.86%)	2 (7.69%)	7 (12.96%)
3-4 years	1 (3.57%)	3 (11.54%)	4 (7.41%)
4-5 years	1 (3.57%)	5 (19.23%)	6 (11.11%)
More than 5 years	21 (75.00%)	14 (53.85%)	35 (64.81%)
Total	28 (100.00%)	26 (100.00%)	54 (100.00%)
Duration of treatment			
1-2 years	0 (0.00%)	3 (11.54%)	3 (5.56%)
2-3 years	5 (17.86%)	5 (19.23%)	10 (18.52%)
3-4 years	1 (3.57%)	3 (11.54%)	4 (7.41%)
4-5 years	1 (3.57%)	4 (15.38%)	5 (9.26%)
More than 5 years	21 (75.00%)	11 (42.31%)	32 (59.26%)
Total	28 (100.00%)	26 (100.00%)	54 (100.00%)
Treatment used			
Typical antipsychotic (Haloperidol)	8 (28.57%)	8 (30.77%)	16 (29.63%)
Atypical antipsychotic (Olanzapine)	20 (71.43%)	18 (69.23%)	38 (70.37%)
Total	28 (100.00%)	26 (100.00%)	54 (100.00%)

Ethical approval for the study was obtained from the Sudan Gezira University the Research Ethics Committee (Approval Referans Number C.C/K.T.D.A/T.L.A.B dated September 17, 2009).

MRI Acquisition

Structural magnetic resonance imaging was conducted using a 1.5 Tesla SIEMENS scanner (Production city) at the National Ribat University, Sudan. T1 weighted sequences were acquired through a three-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) protocol, which enables high contrast between gray and white matter within a relatively short scan duration. Imaging parameters included a slice thickness of 1.0 mm, a field of view of 250 mm (read) × 192 mm (phase), repetition time (TR) of 1657 ms, echo time (TE) of 2.95 ms, and a bandwidth of 180 Hz/pixel. The flip angle was set to 15°, echo spacing was 7.5 ms, with 100% phase resolution and 50% slice resolution. The total acquisition time was approximately 5 minutes and 18 seconds.

Analysis of MRI

All participants’ DICOM images were subjected to blinded analysis through a series of dedicated software applications.

1. ImageJ software (Figure 1); following re-slicing and re-orientation, all images were converted to the standardized Analyze 7.5 format for further analysis.
2. Brain Suite software (Figure 2); was utilized to process the images, which had been previously converted into Analyze format and imported into the structural brain analysis environment. The processing involved the following sequential steps:
 - The skull stripping phase was manually inspected and, when necessary, adjusted to ensure accurate demarcation of brain tissue boundaries.
 - The subsequent procedures including hemispheric separation, surface generation, and volume registration were executed automatically by the software.
 - After completing visual quality control, the software computed the volumetric values for the regions of interest (ROIs).

The volumes of the parietal lobes, gray and white matter, cortical pial surface area, and cortical thickness of both the frontal and parietal lobes were automatically extracted. All measurements were recorded in a central datasheet specifically designed for this study, and volumetric calculations were subsequently performed.



Figure 1. ImageJ software program

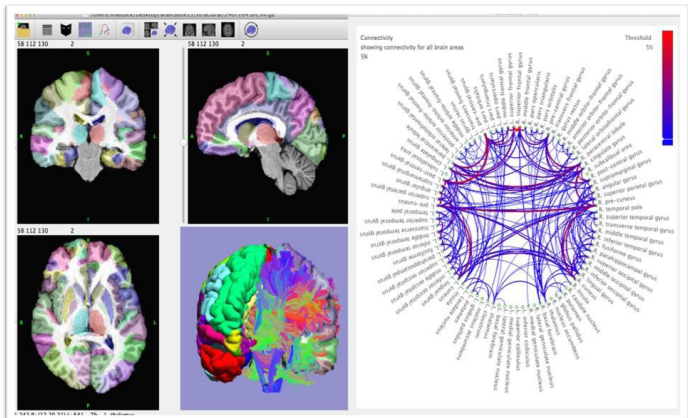


Figure 2. BrainSuite software program

RESULTS

Analysis of Demographic Differences Between Individuals with Schizophrenia and Healthy Controls

The one-way analysis of variance (ANOVA) revealed no statistically significant differences in age or body mass index (BMI) between male and female participants across both control and schizophrenia groups ($p>0.050$). Similarly, chi-square analysis indicated no significant variation in gender distribution between the groups ($p>0.050$).

Assessment of Intracranial Volume (ICV)

Intracranial volume was found to be significantly higher in males compared to females in both patient and control groups ($p\leq0.050$). Furthermore, participants with schizophrenia exhibited reduced ICV in comparison to healthy controls ($p\leq0.050$). The mean difference in ICV between the schizophrenia and control groups was calculated as 88.78 cm^3 .

Analysis of Parietal Lobe Structures

To assess variations in parietal lobe parameters between the groups, a mixed-effects repeated measures ANCOVA was conducted. This model controlled for covariates including intracranial volume, age, and treatment status. Hemisphere side was treated as a within subject factor, while case status (patient/control) and gender were treated as between-subject factors.

Then, we found ICV as significant covariates for volumes of the parietal lobe, parietal gray and white matter and cortical area pial of parietal lobe. We found age as significant covariates for volumes of the parietal gray matter. For thickness of parietal lobe we found no significant covariates. We made our analysis with a correcting of significant covariates.

Volume of parietal lobe: A statistically significant difference was observed between the patient group and the control group ($F(1; 131) = 16.756, p<0.001$). Moreover, we found no differences between right and left side in patients and controls ($F(1; 131) = 0.438, p=0.509$) (Table 3).

Table 3. Comparison of mean volumes (cm³±SD) of parietal lobe between groups			
Group	Right	Left	Total
Male control	66.68±5.58	63.93±5.40	130.61±9.80
Male schizophrenic	61.73±6.48 (p=0.039*)	56.71±5.25 (p=0.039*)	118.45±10.72 (p<0.001*)
Female control	63.83±5.94	60.23±5.62	124.06±10.75
Female schizophrenic	57.04±5.59 (p=0.039*)	54.06±4.60 (p=0.039*)	111.10±9.81 (p<0.001*)
Control (All)	65.48±5.88	62.37±5.76	127.85±10.65
Schizophrenic (All)	59.5±6.47 (p<0.001*)	55.46±5.09 (p<0.001*)	114.97±10.86 (p<0.001*)
SD: standard deviation; P-values (p<0.05) are highlighted in*			

Volume of gray matter: Statistically significant difference was observed between the patient group and the control group ($F(1; 130) = 5.952, p = 0.016$). Moreover, we found no differences between right and left side in patients and controls ($F(1; 130) = 1.103, p = 0.296$) (Table 4).

Volume of white matter: There was significant difference between patients and controls ($F(1; 131) = 12.797, p < 0.001$), also we found significant difference between sex ($F(1; 131) = 6.794, p = 0.010$). Then we made pairwise comparisons and found significant differences between male controls and male patients ($p = 0.039$). Additionally, we found no differences between right and left side in patients and controls ($F(1; 131) = 0.079, p = 0.779$) (Table 4).

Table 4. Comparison of mean volumes (cm³±SD) of gray and white matter of parietal lobe between groups						
Group	Grey matter right	Grey matter left	Grey matter total	White matter right	White matter left	White matter total
Male control	41.82±3.73	39.52±3.15	81.34±6.15	24.86±2.97	24.40±3.30	49.27±5.85
Male schizophrenic	39.69±4.57 (p=0.039*)	35.61±3.35 (p=0.039*)	75.30±7.38 (p=0.016*)	22.04±2.55 (p=0.039*)	21.11±2.50 (p=0.039*)	43.15±4.60 (p<0.001*)
Female control	39.76±4.02	36.95±3.36	76.72±6.73	24.07±2.97	23.28±3.19	47.34±5.97
Female schizophrenic	35.94±3.59 (p=0.039*)	33.43±3.24 (p=0.039*)	69.37±6.50 (p=0.016*)	21.10±2.56 (p=0.039*)	20.63±2.00 (p=0.039*)	41.73±4.37 (p<0.001*)
Control (All)	40.95±3.97	38.44±3.47	79.40±6.77	24.53±2.98	23.93±3.29	48.46±5.94
Schizophrenic (All)	37.92±4.51 (p=0.016*)	34.57±3.45 (p=0.016*)	72.49±7.54 (p=0.016*)	21.59±2.58 (p=0.010*)	20.88±2.27 (p=0.010*)	42.47±4.51 (p=0.010*)
SD: standard deviation; P-values (p<0.05) are highlighted in*						

Cortical pial surface area: No statistically significant difference was found between the patient and control groups ($F(1; 131) = 3.151, p = 0.078$). Moreover, we found no differences between right and left side in patients and controls ($F(1; 131) = 0.372, p = 0.543$) (Table 5).

Thickness of parietal lobe: There was significant difference between patients and controls ($F(1; 132) = 4.313, p = 0.040$). Moreover, we found no differences between right and left side in patients and controls ($F(1; 132) = 0.059, p = 0.808$) (Table 5).

Table 5. Comparison of mean cortical pial surface area (cm²±SD) and parietal lobe thickness (mm±SD) between groups						
Group	Cortical pial area right	Cortical pial area left	Cortical pial area total	Thickness right	Thickness left	Thickness total
Male control	185.95±14.89	176.12±15.54	362.07±26.77	4.25±0.22	4.27±0.24	4.26±0.21
Male schizophrenic	179.25±14.82 (p=0.078)	162.36±13.73 (p=0.078)	341.60±24.43 (p=0.078)	4.30±0.20 (p=0.040*)	4.32±0.22 (p=0.040*)	4.31±0.20 (p=0.040*)
Female control	177.62±15.32	166.25±14.70	343.87±26.46	4.20±0.18	4.23±0.21	4.21±0.18
Female schizophrenic	165.46±15.48 (p=0.078)	155.50±11.59 (p=0.078)	320.96±25.94 (p=0.078)	4.34±0.19 (p=0.040*)	4.27±0.22 (p=0.040*)	4.31±0.18 (p=0.040*)
Control (All)	182.45±15.55	171.97±15.88	354.42±27.99	4.23±0.21	4.25±0.23	4.24±0.20
Schizophrenic (All)	172.72±16.53 (p=0.078)	159.11±13.11 (p=0.078)	331.83±27.01 (p=0.078)	4.32±0.20 (p=0.040*)	4.30±0.22 (p=0.040*)	4.31±0.19 (p=0.040*)

DISCUSSION

At present, the diagnostic utility of neuroimaging techniques in schizophrenia remains limited, primarily aiding in the detection of structural brain abnormalities in a small subset of individuals with secondary forms of psychosis. Despite this limitation, neuroimaging modalities hold considerable promise for elucidating the potential trajectory of the illness. Moreover, these techniques provide valuable tools for evaluating the effects of therapeutic interventions, including both pharmacological treatments and cognitive-based therapies (20).

The present study demonstrates a significant reduction in parietal lobe volume in patients with schizophrenia compared to healthy individuals (21). Given that the duration of illness and treatment exceeded five years in the majority of our sample (75.92% and 68.52%, respectively), our findings are consistent with those of Olabi et al., who reported a progressive decline in whole-brain volume, gray matter, and parietal white matter volume in patients with schizophrenia relative to healthy controls (22).

Significant differences were observed between patients and controls in parietal lobe volume, as well as in parietal

gray and white matter volumes. Although the parietal lobe has not been investigated as extensively as the temporal lobe (23), our findings are consistent with several-though not all MRI studies (23,24). Moreover, previous research has also reported parietal volume reductions in individuals with schizophrenia, including those experiencing a first episode of the illness (25).

A voxel-based morphometry (VBM) investigation revealed reductions in gray matter volume within the temporal, frontal, occipital, and parietal lobes (26). Another VBM-based study reported that schizophrenia exerts its most prominent structural impact on white matter, suggesting that white matter may represent the primary region affected in the pathophysiology of schizophrenia (27). Additionally, certain studies have noted structural atrophy within the parietal lobe particularly involving the cingulate and supramarginal gyri as well as in the occipital lobe. However, such findings appear to be relatively uncommon and are typically associated with more advanced stages of the disorder (28).

The parietal lobe accounts for approximately one-quarter of the human brain and, with the exception of its somatosensory subregion, forms part of the heteromodal association cortex. This region plays a critical role in integrating visual, auditory, and tactile sensory inputs and coordinating appropriate behavioral responses (29).

Findings from the present study indicate a reduction in total parietal lobe volume, as well as in both gray and white matter volumes, in patients with schizophrenia when compared to healthy controls. We suggest that these structural changes may contribute to the pathophysiologic mechanisms underlying the disorder.

In the present study, no statistically significant differences were identified between the right and left parietal lobes regarding gray and white matter volumes in either the schizophrenia group or the healthy controls. This result may indicate a disruption of the typical left-hemispheric dominance, a neuroanatomical characteristic considered essential for normative language development. These results align with previous research suggesting that individuals with schizophrenia often exhibit either a reversal of hemispheric lateralization toward the right hemisphere or a general reduction in left-lateralized language processing (30-32).

Multiple neuroimaging studies have documented alterations in the typical cerebral torque configuration in individuals with schizophrenia compared to healthy controls (33). This asymmetry, normally reflected in the greater width of the right frontal and left occipital lobes relative to the opposite hemispheres, appears to be disrupted in schizophrenia. In healthy populations, cerebral torque contributes to establishing asymmetrical brain connectivity patterns (34). This structural asymmetry is thought to facilitate information flow within

the brain, typically progressing from the left occipito-temporo-parietal region to the right occipito-temporo-parietal region, then to the right dorsolateral prefrontal cortex, and finally to the left dorsolateral prefrontal cortex. Consequently, it has been proposed that core features of schizophrenia may be linked to a disruption in this left-hemisphere-dominant network involved in language processing (34,35). These findings suggest potential neuropathological mechanisms underlying the observed loss of hemispheric lateralization in patients with schizophrenia.

In the present study, individuals with schizophrenia demonstrated no statistically significant differences in cortical pial surface area of the parietal lobes compared to controls ($F(1,131)=3.151$, $p=0.078$), nor any lateral asymmetry in either group ($p=0.543$). In contrast, parietal cortical thickness was significantly reduced in the schizophrenia group relative to controls ($F(1,132)=4.313$, $p=0.040$), again without side differences ($p=0.808$). These observations suggest that whereas the overall surface area of the parietal cortex remains unaffected, the cortex itself is subtly thinner in patients.

This pattern aligns with the broader neuroimaging literature, which shows that cortical thinning is a more robust and widespread feature of schizophrenia than surface area reduction, the latter being more regionally variable or even preserved in some cohorts. Meta-analytic data from the ENIGMA consortium report robust reductions in cortical thickness (Cohen's $d \approx -0.53$ bilaterally) and smaller, more globally distributed reductions in surface area ($d \approx -0.25$), with the strongest effects observed in the frontal and temporal regions, and somewhat less pronounced changes in the parietal areas, as reported by van Erp et al. (36).

Similarly, in a large cohort of first episode, antipsychotic-naïve individuals with schizophrenia, significant cortical thinning was observed across the frontal and temporal cortices, while surface area showed no group differences. This reinforces the pattern of cortical thickness being the principal driver of volumetric change (37,38).

Studies focusing on high-risk or unaffected familial cohorts have shown preserved or even slightly increased cortical thickness alongside reduced surface area in fronto-parietal regions, supporting the idea that surface area alterations may reflect genetic liability, whereas thinning may be more closely tied to illness manifestation or progression (38,39).

By contrast, our findings in a Sudanese sample demonstrate preserved parietal cortical pial surface area despite reduced thickness. The consistency of lateral symmetry in both parameters further underscores the generalized rather than focal nature of these morphological differences.

Strengths of the Study

This study is among the first to investigate parietal lobe morphology in individuals with schizophrenia within a Sudanese population, addressing a major gap in African neuroimaging data. The use of high-resolution MRI and automated brain segmentation software allowed for objective assessment of gray matter, white matter, cortical thickness, and pial surface area. Statistical control for important confounders such as age, intracranial volume, and treatment status through repeated measures ANCOVA enhanced the validity of the results. Including both sexes and analyzing sex differences further strengthened the generalizability. By distinguishing between different parietal tissue components, the study provides a detailed profile of schizophrenia-related structural alterations.

Limitations of the Study

The cross-sectional design prevents conclusions about disease progression or causality. The moderate sample size, while adequate, limits subgroup analyses and statistical power. Minor inaccuracies may arise from automated segmentation tools, particularly in populations underrepresented in their development. The absence of cognitive or neuropsychological assessments restricts the ability to link structural changes to functional outcomes. Finally, the findings may not be generalizable beyond similar demographic and clinical settings, and replication in other populations is encouraged.

CONCLUSION

Patients demonstrated reduced mean parietal lobe volume relative to controls. In addition, average volumes of parietal gray and white matter were lower in the schizophrenia group. While the cortical pial surface area of the parietal cortex did not differ significantly between groups, cortical thickness in this region was notably reduced in patients.

Since large numbers of studies have showed variable results in measurements of the brain volume in schizophrenia, which may reflect effects of age, gender, illness chronicity, and neuroleptic medications as confounding factors in the pathophysiology of schizophrenia, future studies may gain greater insight by focusing on more homogeneous patient populations, incorporating analyses of sex-related differences, and performing detailed parcellation and assessment of specific subregions within the parietal lobes.

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Nursing Care Perceptions of the Patients in The Chest Diseases Inpatient Clinic

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Abstract

Aim: Nursing care constitutes an important element of healthcare provider and patient satisfaction because the nature of the service provided requires intense and close communication with patients. In this study, the goals were to determine patient satisfaction and the effects of patient factors contributing to it inpatients in a chest disease clinic.

Material and Method: Our descriptive and cross-sectional study included the patients who had been hospitalized in our clinic. Details about the patients have been recorded through one-on-one interviews using the "Patient Information Form" and "Patient's Perception of Nursing Care Scale". The relevance between patients' socioeconomic status and nursing care perception has been investigated.

Results: Eighty-six patients treated as inpatients in our Chest Diseases Clinic between March and May 2021 were included. The mean age was 67.4 ± 12.5 years, with 59.3% male and 40.7% female. The average hospital stay was 6.4 ± 5.9 days. No significant relationship was found between age, sex, and patient satisfaction ($p=0.230$ and $p=0.350$). However, higher education levels were linked to lower satisfaction ($p=0.020$). Overall, patient satisfaction was higher than the general average.

Conclusion: While the level of satisfaction with nursing is generally independent of age and gender; it is directly related to the level of education and the level of expectation from health care. Patients' satisfaction level can be increased with an approach, communication and care services appropriate to patient characteristics.

Keywords: Nursing care, patient satisfaction, health care

INTRODUCTION

In today's world, the competitive environment surrounding the delivery of healthcare services is increasingly intensifying. Changes in patient expectations, healthcare costs, and the growing awareness among administrators, healthcare professionals, and patients have all contributed to making patient satisfaction a critical component of healthcare services (1). With the growing awareness, interest in patient satisfaction has gained increasing importance in recent years. Patient satisfaction is regarded as an indicator of the quality of the healthcare service delivery process.

Nurses are the healthcare professionals with whom patients interact most frequently during healthcare processes, including their care and treatment. Nurses play an active role in the provision of healthcare services and they make significant contributions to the maintenance of individual health, the treatment of illnesses, and rehabilitation. They

provide continuous care throughout the patient's hospital stay and are the most consistently accessible members of the healthcare team from the patients' perspective (2).

Improving the quality of nursing care, shaped by the interplay of patient expectations and perceptions, requires that the healthcare team—especially nurses—be aware of how patients perceive nursing care and of the factors that affect these perceptions (3). Patient satisfaction is influenced by the patient's expectations of the healthcare institution and nursing care, as well as by their past experiences. When patients are consistently able to interact with the same nurses with whom they have previously established communication upon returning to a healthcare facility, their satisfaction tends to increase. In addition, the job satisfaction of nurses providing healthcare services also influences patients' satisfaction with the nursing care they receive. A nurse who expresses being overworked or having workplace-related issues can negatively affect patients' levels of

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satisfaction and their perceptions of care. Moreover, the work environment in which the nursing profession is practiced stands out as an important indicator of how patients perceive the quality of care (4).

This study aimed to identify the perceptions of nursing care among inpatients receiving treatment in the Department of Pulmonology, to improve service quality, to determine deficiencies in nursing care services, and to identify aspects that need further development. In this way, the findings may contribute to the planning and improvement of pre-graduation education for nursing students, as well as in-service training programs for currently practicing nurses.

MATERIAL AND METHOD

Type of Study

The study was designed as a cross-sectional study.

Study Population and Sampling

The study was conducted in the Chest Diseases Clinic of our hospital between March and May 2021. The study population consisted of 102 patients who were hospitalized for treatment during this period, while the sample included 86 patients who met the inclusion criteria (being over 18 years of age, being literate, and being willing to participate in the study). Sixteen patients who were unable to provide informed consent due to communication or cognitive impairments were excluded from the study. In our study, a power analysis conducted using (G*Power 3.1.9.4) indicated that a sample size of 85 patients would be required to achieve 80% statistical power with a 95% confidence interval.

Data Collection

The 'Patient Information Form' and the 'Patient Perception of Nursing Care Scale (PPNCS)' were administered face-to-face to patients hospitalized in the Chest Diseases Unit.

Data Collection Tools

Patient Information Form:

In the Patient Information Form, the patients included in the study were grouped socio-demographically based on their name and surname, file number, age, gender, length of hospital stay, education level, marital status, occupation, income level, place of residence, number of hospitalizations in the past year, presence of comorbidities, number of patients in the room, reason for choosing the hospital, and presence of a companion. Patients were categorized into age groups as follows: 19–40, 41–65, 66–80, and over 80 years old. Patients were categorized based on length of hospital stay into the following groups: 0–3 days, 4–7 days, 8–14 days, and more than 14 days. Educational status was categorized as illiterate, literate, primary education, high school, and university level. In the assessment of income status, participants were categorized as having income lower than expenses, income equal to expenses, income higher than expenses, or no income. Based on place of residence, patients were categorized as residing in a city center, district, township,

or rural village. The number of hospitalizations within the last year was categorized as: one, two, and three or more admissions. Patients were grouped based on the number of individuals in the hospital room as either one or two persons. Patients were classified based on their reason for hospital preference, such as recommendation, physician preference, emergency admission, referral, being under follow-up care, previous hospitalization experience, allowance of a companion, and presence of a companion.

Patient Perception of Nursing Care Scale:

The Patient Perception of Nursing Care Scale (PPNCS) is a 15-item, five-point Likert-type scale designed to measure patients' perceptions of nursing care, originally developed by Dozier et al (5). The Turkish adaptation of the scale was conducted by İ.G. Çoban, and its validity and reliability have been demonstrated (6). Participants responded to the items by selecting one of the following options: strongly disagree (1), disagree (2), neutral (3), agree (4), and strongly agree (5). The scores of each item on the scale were summed and then converted to a score out of 100, resulting in a total score ranging from 0 to 100. A total score of 100 was interpreted as an indication of complete satisfaction with all aspects of the nursing care received.

Statistical Analysis of the Data

Statistical analyses of the study data were performed using SPSS Statistics version 21. Descriptive statistical measures used in the study were frequency, percentage, mean, median (with interquartile range), and standard deviation. The Student's t-test was used to compare numerical variables with normal distribution, while the Mann–Whitney U test was applied for variables that did not follow a normal distribution. The comparison of categorical variables was performed using the Chi-square test. In all statistical analyses, a p-value <0.05 was accepted as the threshold for statistical significance.

Ethical Considerations of the Study

The study was approved by the Health Sciences Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine (Approval date: February 24, 2021; Decision number: 20.478.486). All patients provided written informed consent. The study adhered to the principles of the Declaration of Helsinki and the guidelines of the approving ethics committee.

RESULTS

The study sample comprised 86 patients hospitalized in a pulmonary diseases clinic. The mean age was 67.4±12.5 years, with a predominance of male patients (59.3%). The average length of hospital stay was 6.4±5.9 days. Most participants were married (80.2%) and retired or homemakers by occupation. Educational attainment was generally low; 48.6% of patients had completed only primary school or had no formal education, while only 9.3% were university graduates.

Regarding economic status, nearly half (46.5%) reported income below their expenses, and 15.1% were dependent on external support. A substantial portion of patients resided

in non-urban areas—towns (17.5%), villages (20.9%), or districts (27.9%)—while 33.7% lived in the provincial center. Most participants (75.6%) had been hospitalized more than once in the past year, and a high proportion (88.4%) had at least one chronic comorbidity, the most common being hypertension (31.4%), heart failure (26.7%), and chronic obstructive pulmonary disease (COPD) (22.1%). The primary factors influencing hospital preference were emergency medical needs (31.4%), physician choice (18.6%), and continuity of follow-up care (12.8%). More than half of the patients (59.3%) were accompanied by a caregiver during hospitalization (Table 1).

Table 1. Sociodemographic Characteristics of the Patients (n=86)		
Variable	Categories	n (%)
Age (mean±SD)	—	67.4 ±12.5
Gender	Male/Female	51 (59.3)/35 (40.7)
Marital status	Married/Single	69 (80.2)/17 (19.8)
Education	Illiterate/Literate/Primary/High school/University	9 (10.4)/17 (19.8)/33 (38.4)/19 (22.1)/8 (9.3)
Occupation	Civil servant/Worker/Self-employed/ Farmer/Retired/Housewife/Other	11 (12.8)/7 (8.1)/9 (10.5)/7 (8.1)/22 (25.6)/ 26 (30.2)/4 (4.7)
Income	Lower/Equal/Higher/None	40 (46.5)/24 (27.9)/9 (10.5)/13 (15.1)
Residence	City/District/Town/Village	29 (33.7)/24 (27.9)/15 (17.5)/18 (20.9)
Length of stay (days)	—	6.4±5.9
Hospitalizations (last year)	1/2/≥3	21 (24.4)/32 (37.2)/33 (38.4)
Comorbidities	Yes/No	76 (88.4)/10 (11.6)
Comorbidity types	COPD/Asthma/Hypertension/Diabetes/Lung cancer/ Other cancers/PLD/HF/CAD/CTD/Other	19/5/27/15/9/4/13/23/16/7/5
Room type	Single/Double	13 (15.1)/73 (84.9)
Reason for hospital choice	Emergency/Physician/Follow-up /Recommendation/ Referral/Previous admission/ Companion allowed	27 (31.4)/16 (18.6)/11 (12.8)/9 (10.5)/ 7 (8.1)/11 (12.8)/5 (5.8)
Companion presence	Yes/No	51 (59.3)/35 (40.7)
SD: standard deviation, n: number, COPD: chronic obstructive pulmonary disease, HT: hypertension, DM: diabetes mellitus, Ca: cancer, PLD: parenchymal lung disease, HF: heart failure, CAD: coronary artery disease, CTD: connective tissue disease		

A total of 65 patients (75.6%) stated that nurses responded to them promptly, 69 (80.2%) reported that nurses gave their full attention during care, and 58 (67.4%) indicated that nurses helped them become more aware of the realities of their illness. These rates were found to be higher among patients with chronic conditions and those with a history of more than three hospitalizations within the past year (Table 2).

Table 2. Patients' Perceptions of Nursing Care Scale (PPNCS) results						
Item	Strongly disagree (%)	Disagree (%)	Neutral (%)	Agree (%)	Strongly agree (%)	Mean score
They helped me become more realistic.	3.4	7.0	9.3	19.8	60.5	84.7
They considered more than just my basic needs.	10.5	9.3	5.8	15.1	59.3	83.1
They responded to my needs immediately.	2.3	4.6	7.0	10.5	75.6	89.9
They gave me their full attention during care.	1.2	8.1	1.2	9.3	80.2	91.4
They consulted me before doing most things.	4.6	8.1	4.6	12.8	69.8	87.8
They made me feel comfortable in the hospital.	9.3	10.5	12.8	18.6	48.8	74.2
They informed me about things I didn't know about the hospital.	5.8	4.6	17.4	16.3	55.9	79.3
I'm confident they notified the right people about my needs and wishes.	2.3	2.3	19.8	25.5	51.1	77.2
I feel confident they would be there when I needed them.	1.2	3.5	9.3	10.5	75.5	89.8
I feel they understood what my illness means to me.	3.5	8.1	11.6	9.4	67.4	85.7
I know some problems were prevented thanks to nurses' efforts.	4.6	9.3	9.3	20.9	55.9	81.0
They helped me cope with fears related to my illness.	10.5	13.9	8.1	22.1	45.4	73.9
Their explanations helped me feel at ease.	4.6	1.2	24.4	27.9	41.9	71.8
They comforted me during treatments.	2.3	5.8	5.8	20.9	65.2	86.2
Thanks to the nurses, I felt well cared for.	3.5	3.5	12.8	11.6	68.6	87.3
PPNCS: Patient Perception of Nursing Care Scale						

The analysis of Patients' Perceptions of Nursing Care Scale (PPNCS) scores according to demographic and clinical variables revealed statistically significant differences, particularly when evaluated by education and income levels. A clear inverse relationship was observed, indicating that as the level of education increased, perceived satisfaction with nursing care decreased ($p=0.020$). Illiterate patients reported the highest satisfaction levels (89.7%), followed by those with basic literacy (89.5%), primary school graduates (88.9%), high school graduates (87.4%), and university graduates (73.1%). Similarly, income level was found to significantly impact satisfaction, with lower-income patients reporting higher satisfaction levels ($p=0.030$).

Geographic location also played a role: patients residing in rural areas (villages: 92.2%, towns: 89.4%) reported higher satisfaction compared to those living in urban centers (districts: 89.0%, provincial centers: 82.7%; $p=0.021$).

The duration of hospitalization had minimal effect on

satisfaction levels among patients staying up to 14 days (0–3 days: 88.5%, 4–7 days: 88.3%, 8–14 days: 87.9%). However, a notable decline in satisfaction was observed among those hospitalized for more than 14 days (81.7%).

Comorbidity status significantly influenced satisfaction; patients with additional chronic illnesses reported higher satisfaction scores ($p=0.035$). Additionally, a positive correlation was observed between the frequency of hospitalizations within the past year and satisfaction with nursing care—patients hospitalized three times or more expressed the highest satisfaction levels ($p=0.041$).

Lastly, room occupancy emerged as another determinant: patients in single-occupancy rooms reported significantly higher satisfaction (94.8%) compared to those in double-occupancy rooms (87.5%; $p=0.025$) (Table 3).

In the evaluation according to age groups and gender, no significant differences were found in satisfaction scores ($p=0.230$ and $p=0.350$, respectively).

Table 3. Relationship between patients' sociodemographic characteristics and PPNCS scores				
Variable		n (%)	PPNCS Mean	P value
Age (years)	19–40	11 (12.8)	85.2	0.230
	41–65	23 (26.7)	86.1	
	66–80	38 (44.2)	87.9	
	>80	14 (16.3)	88.4	
Gender	Male	51 (59.3)	88.9	0.350
	Female	35 (40.7)	87.8	
Length of stay (days)	0–3	18 (20.9)	88.5	0.165
	4–7	36 (41.9)	88.3	
	8–14	23 (26.7)	87.9	
	>14	9 (10.5)	81.7	
Marital status	Married	69 (80.2)	88.6	0.201
	Single	17 (19.8)	90.2	
Education	Illiterate	9 (10.4)	89.7	0.020*
	Literate	17 (19.8)	89.5	
	Primary	33 (38.4)	88.9	
	High school	19 (22.1)	87.4	
	University	8 (9.3)	73.1	
Occupation	Civil servant	11 (12.8)	84.4	0.070
	Worker	7 (8.1)	86.2	
	Self-employed	9 (10.5)	86.5	
	Farmer	7 (8.1)	88.2	
	Retired	22 (25.6)	88.7	
	Housewife	26 (30.2)	89.3	
	Other	4 (4.7)	83.5	
Income	Less than expenses	40 (46.5)	88.8	0.030*
	Equal to expenses	24 (27.9)	86.4	
	More than expenses	9 (10.5)	73.2	
	No income, supported	13 (15.1)	90.3	

COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HF: heart failure, HT: hypertension, n: number, PPNCS: Patient Perception of Nursing Care Scale

Table 3. Relationship between patients' sociodemographic characteristics and PPNCS scores				
Variable		n (%)	PPNCS Mean	P value
Residence	City center	29 (33.7)	82.7	0.021*
	District	24 (27.9)	89.0	
	Town	15 (17.5)	89.4	
	Village	18 (20.9)	92.2	
Hospitalizations (last year)	One	21 (24.4)	82.5	0.041*
	Two	32 (37.2)	86.3	
	≥3	33 (38.4)	91.3	
Comorbidities	Present (e.g., COPD, HT, DM, HF)	76 (88.4)	89.7	0.035*
	Absent	10 (11.6)	79.6	
Room occupancy	Single	13 (15.1)	94.8	0.025*
	Double	73 (84.9)	87.5	
Hospital preference reason	Recommendation	9 (10.5)	89.6	0.075
	Doctor	16 (18.6)	89.0	
	Emergency	27 (31.4)	88.3	
	Referral	7 (8.1)	88.4	
	Follow-up	11 (12.8)	88.5	
	Previous admittance	11 (12.8)	89.1	
	Companion allowed	5 (5.8)	87.2	
Companion presence	Yes	51 (59.3)	88.9	0.190
	No	35 (40.7)	88.5	
COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HF: heart failure, HT: hypertension, n: number, PPNCS: Patient Perception of Nursing Care Scale				

DISCUSSION

In this study, which aimed to determine the satisfaction levels of inpatients receiving care in a pulmonology clinic with nursing services and to reflect their perceptions and opinions regarding nursing care, the values obtained were found to be above the overall average (7).

In our study, differences were observed in the mean PPNCS scores when classified according to length of hospital stay, educational level, income status, place of residence, number of hospitalizations within the past year, presence of comorbidities, and number of patients in the room. Among these parameters, only length of stay—specifically in patients hospitalized for more than 14 days—was not statistically significant, whereas the others showed statistically significant differences. The lower mean PPNCS score among patients with a hospital stay longer than 14 days may be due to the smaller number of patients in this group (n=9, 10.5%) compared to others, or it may reflect the negative impact of prolonged hospitalization on patient satisfaction.

An analysis based on educational status revealed an inverse correlation between the level of education and satisfaction with nursing care; as the educational level increased, the mean scores on the Patient Satisfaction with Nursing Care Scale (PPNCS) demonstrated a declining trend (p=0.020). This situation may be attributed to the fact that individuals with higher levels of education tend to

have greater expectations. As the overall educational level of society increases, individuals become more culturally informed, more capable of critically evaluating the services they receive, and more actively involved in their own care processes. Consequently, this situation may lead to the emergence of patients with evolving and increasingly diverse expectations regarding the quality and delivery of healthcare services. It is emphasized that satisfaction with nursing care is closely linked to patient expectations, which tend to increase in parallel with higher levels of education. Consequently, it is often observed that patients with higher educational backgrounds report lower levels of satisfaction. As a result, the expectations of patients regarding the quality of healthcare services are rising, which directly influences their perception of satisfaction. A review of similar studies in the literature reveals notable variations in the findings. While some studies report results consistent with those of the present study (8,9), others have yielded differing outcomes (10,11).

In the gender-based analysis conducted in our study, the mean scores on the Patient Satisfaction with Nursing Care Scale (PPNCS) were found to be similar for both male and female patients. The reason for this may be that both male and female patients have similar expectations and perceptions of healthcare services, especially within the same clinical and cultural context; this could explain why expectations between men and women were similar in our study. However, some studies in the literature have reported

that female patients tend to express higher levels of satisfaction compared to their male counterparts (10,12). This difference may be attributed to the traditional societal roles assigned to women from an early age, particularly their primary responsibility in meeting basic needs such as clothing and nutrition.

When the mean scores on the Patient Satisfaction with Nursing Care Scale (PPNCS) were evaluated according to age, no significant differences were observed ($p=0.230$). The lack of a significant difference according to age in our study may be explained by the sample size or the influence of cultural factors. However, a review of related studies reveals varying results in the literature. While the findings of some studies are consistent with those of the present study (13,14), other studies have reported that satisfaction levels tend to increase with advancing age (14,15).

In our study, the analysis based on the presence of a companion revealed no significant difference in patient satisfaction between those with and without a companion (88.9% vs. 88.5%, $p=0.190$). This finding may be explained by patients' ability to independently meet their personal needs and perform self-care.

The primary limitation of our study is that it was conducted exclusively with inpatients in the pulmonology clinic, meaning that the participants represent only a small segment of the overall patient population. However, the adequacy of the sample size and the consistent, homogeneous distribution of the results support the reliability of our findings. A notable strength of this study is that it represents one of the pioneering efforts to investigate patient satisfaction with nursing care services specifically in pulmonology clinics, a subject that remains underexplored in the literature. Future research should include other medical specialties, compare satisfaction levels across various disciplines, and more clearly identify the factors influencing patient satisfaction through broader, interdisciplinary investigations.

CONCLUSION

In conclusion, the overall mean score on the Patient Satisfaction with Nursing Care Scale (PPNCS) was found to be high. However, the analysis revealed that patients with higher levels of education and income, as well as those residing in urban areas, reported comparatively lower satisfaction levels. The findings highlight the importance of tailoring nursing care to the specific characteristics of each patient. Personalized care approaches, effective communication, and needs-based nursing interventions can significantly enhance patient satisfaction. These results may serve as a guide for improving nursing service planning and promoting a more patient-centered approach in clinical practice.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: The study was approved by the Health Sciences Ethics Committee of the Manisa Celal Bayar University Faculty of Medicine (Approval date: February 24, 2021; Decision number: 20.478.486).

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Evaluation of Colonoscopic Procedures Performed in A University Hospital According to International Standards

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Abstract

Aim: Colonoscopy continues to be the most dependable technique for early detection of colorectal cancer, one of the most prevalent cancers globally. To enhance the effectiveness of colonoscopic procedures, various international quality benchmarks have been established. This study aimed to assess whether colonoscopies conducted at the Endoscopy Unit of the Gastroenterology Clinic at Firat University Hospital met internationally recognized quality standards.

Material and Method: This retrospective study analyzed 2,805 colonoscopy procedures performed between 2015 August and 2019 January. International quality indicators were used for evaluation. Due to the lack of recorded procedure times prior to November 2018, the data were categorized into two periods: 2015 August –2018 October and 2018 November –2019 January.

Results: From August 2015 to October 2018, the adenoma detection rate was 36% in males and was 26.4% in females. From November 2018 to January 2019, the adenoma detection rate (ADR) increased to 27.5% in females and 43% in males. The cecal intubation rate was 82% in the earlier period and rose slightly to 84.4% in the latter. Sedation was administered in 91.4% of procedures during the first period and in 98% during the second. Procedure duration, recorded only in the latter period, averaged 13.6 minutes.

Conclusion: The ADR observed in this study align with international benchmarks; however, cecal intubation and colorectal cancer detection rates were below the recommended standards. These findings indicate that procedural improvements are necessary to meet international quality criteria more consistently.

Keywords: Colonoscopy, colorectal cancer, polyp, adenoma detection rate, quality indicators

INTRODUCTION

Colorectal cancers remain a major contributor to global cancer-related illness and death, responsible for about 9.4% of all cancer fatalities. Its global incidence continues to rise, largely due to environmental risk factors associated with changes in lifestyle and dietary habits. Known risk factors include advanced age, smoking, alcohol use, obesity, inflammatory bowel disease, a high-fat diet, exposure to radiation, genetic predispositions, and the presence of adenomatous polyps (1-3).

Improvements in screening programs, combined with the early identification and management of precancerous lesions, have played a significant role in reducing mortality associated with colorectal cancer. Screening strategies aim to identify colorectal lesions at an early stage and to prevent malignant transformation by addressing these

lesions before they progress. Colonoscopy plays a central role in these efforts, as it allows for both the detection and removal of premalignant and malignant lesions in a single procedure (4,5). As a result, the demand for colonoscopy has significantly increased, especially in parallel with the expansion of cancer screening programs. Colonoscopy is considered safe and generally well-tolerated by patients when conducted by skilled practitioners (6,7).

Colonoscopy is not only essential for diagnosing colorectal cancer but is also routinely used to investigate symptoms associated with various colonic disorders. Extensive research has demonstrated that colonoscopy, especially when paired with polypectomy, significantly lowers the incidence and mortality rates of colorectal cancer (8-10). Although colonoscopy remains the gold standard for screening, it has certain limitations. To enhance its effectiveness and minimize inter-operator variability, a

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number of quality indicators have been introduced in recent years (11).

The effectiveness of colorectal cancer screening is closely tied to the adherence to established quality benchmarks during colonoscopic procedures. To this end, the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) have defined specific performance benchmarks. Essential quality metrics for colonoscopy include sedation practices, the adenoma detection rate (ADR), and the cecal intubation rate. Research has shown that improved adherence to these criteria leads to higher polyp detection rates and greater success in identifying and treating precancerous lesions. Therefore, maintaining high compliance with these standards is critical to maximizing the effectiveness of colonoscopy (12-15).

The objective of this study was to evaluate whether colonoscopy procedures performed at the Endoscopy Unit of the Gastroenterology Clinic at Firat University Hospital between August 2015 and January 2019 met internationally recognized quality standards. Additionally, the study aimed to identify any deficiencies and propose strategies to enhance procedural quality.

MATERIAL AND METHOD

Ethical approval of study was obtained on 07 .02. 2019 (approval number: 07) from Firat University Ethics Committee, and all procedures were carried out in line with the principles set forth in the 2013 revision of the Declaration of Helsinki.

In this retrospective study, colonoscopic procedures performed over the last three years in the Endoscopy Unit of the Gastroenterology Clinic at Firat University Hospital were evaluated. The analysis focused on quality indicators for colonoscopy as defined by the ASGE and the ESGE. The markers used in this study included the cecal intubation rate, adenoma detection rate, patient comfort (assessed through sedation), and the duration of colonoscopy withdrawal time.

Out of 5,192 colonoscopy cases reviewed during the specified period, 2,805 patients fulfilled the inclusion criteria and were included in the study. These patients were categorized into two groups: Group 1 included 2,655 individuals who underwent colonoscopy prior to November 2018, and Group 2 included 150 patients who underwent colonoscopy between November 2018 and January 2019. Due to the lack of documented colonoscopy durations prior to November 2018, analyses related to procedural time were limited to patients in Group 2.

Exclusion criteria were applied to patients with a known history of cancer, those diagnosed with polyposis syndromes, and individuals under the age of 50.

Demographic data such as age and gender, as well as histopathological findings of polyps removed during colonoscopy, were obtained from hospital records. Colonoscopy reports were reviewed to assess whether

sedation was administered, the type and dosage of sedatives used, adenoma detection rates, and cecal intubation rates. In procedures performed during the last three months of the study period, detailed data regarding procedure duration and sedation protocols were available and included in the analysis.

Additionally, a subset of 450 patients from earlier procedures (more than three months prior) was selected to evaluate sedation practices, adenoma detection, and procedure duration retrospectively, where possible. The reports were also used to determine whether the terminal ileum was visualized and whether cecal intubation was achieved. For patients in whom polyps were identified, pathology reports were examined to classify the polyps and calculate adenomatous polyp detection rates based on histological findings. Similarly, cases with a diagnosis of cancer during colonoscopy were further evaluated through pathology reports.

All collected data were recorded and analyzed to assess the overall quality of colonoscopy procedures performed in the center. Patients were excluded if they underwent emergency colonoscopy, lacked a clear indication for the procedure, required a sigmoidoscopy instead, or had a specific therapeutic reason for colonoscopy.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 21.0 was used for medical records and analyses (IBM Corp., Armonk, NY). A two-sided p-value of less than 0.05 was regarded as statistically significant in all analyses.

Descriptive Statistics

The distribution of continuous variables was assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests, complemented by visual evaluations through histograms and Q-Q plots.

Comparative Analysis

Given the retrospective and observational nature of the study, statistical comparisons were made to evaluate potential differences between two patient groups based on the time period of colonoscopy (Group 1: 2015 August–2018 October; Group 2: 2018 November–2019 January).

Due to non-normal data distribution, continuous variables such as age and colonoscopy duration were compared between groups using the Mann–Whitney U test. Categorical variables—including adenoma detection rate, cecal intubation rate, sedation status, and polyp characteristics—Pearson's Chi-Square or Fisher's Exact Test was employed based on expected cell frequencies.

Subgroup Analyses

Stratified analyses were conducted by gender, evaluating the distribution of histopathological types of polyps (tubular, tubulovillous, villous, hyperplastic) and presence of dysplasia. Comparisons between male and female patients were similarly performed using appropriate non-parametric or categorical tests.

Additionally, the impact of premedication (sedation use) on procedural outcomes—such as cecum and terminal ileum visualization—was assessed using comparative categorical analysis.

RESULTS

The study included a total of 2,805 patients, with 1,538 males and 1,267 females. Among these, 2,655 patients underwent colonoscopy between August 2015 and October 2018, while 150 patients underwent the procedure between November 2018 and January 2019. In the earlier group, 1,457 (54.8%) were male and 1,198 (45.2%) were female; in the latter group, 81 (54%) were male and 69 (46%) were female. The mean age of patients in the August 2015–October 2018 group was 64.1 years, compared to 58.3 years in the November 2018–January 2019 group.

Polyps were identified in 1,425 patients who underwent

colonoscopy during the August 2015–October 2018 period. Among them, 762 (53.5%) were male and 663 (46.5%) were female. In the later period (November 2018–January 2019), polyps were detected in 78 patients, with 33 (42%) being male and 45 (58%) female.

Single polyps were detected in 46.7% of patients in the earlier group and in 48.8% of those in the later group, with no statistically significant difference between the groups ($p>0.05$). Histopathological analysis revealed that the most common type of polyp was tubular, with no significant difference between the two groups ($p>0.05$). Regarding polyp location, 43% of polyps in the earlier group and 41% in the later group were situated in the distal colon, with no statistically significant difference ($p>0.05$). Additionally, no significant difference was found in the proportion of polyps smaller than 1 cm (87.1% vs. 83.4%) (Table 1).

Table 1. Distribution of polyp count, type, size, and localization

Polyp count	August 2015–October 2018		November 2018–January 2019	
	N	(%)	N	(%)
1	573	46.7	38	48.8
2	286	23.3	19	24.4
3	153	12.5	8	10.3
4	91	7.6	6	7.7
5	48	3.9		
6	27	2.2	3	3.9
7	18	1.4	1	1.2
8	6	0.4	1	1.2
9	8	0.6		
10 and above	18	1.4	2	2.5
Polyp type				
Tubular	607	42.6	39	46.9
Tubulovillous	203	14.2	13	15.6
Villous	36	2.5	2	2.4
Hyperplastic	579	40.7	29	35.1
Polyp size				
0–1cm	1240	87.1	65	83.4
1cm and above	185	12.9	13	26.6
Localization				
Proximal	384	26.9	25	32
Distal	612	43	41	52.6
Proximal+ distal	429	30.1	12	15.4

When the polyps detected between August 2015 and October 2018 were analyzed separately by gender, tubular adenomas were identified in 41% of women and 43.7% of men, hyperplastic adenomas in 42.1% of women and 39.5% of men, tubulovillous adenomas in 13.9% of women and 14.5% of men, and villous adenomas in 2.3% of men and 3% of women. There was no statistically significant difference observed between male and female participants.

For colonoscopies conducted between November 2018 and January 2019, tubular adenomas were found in 57.1% of women and 41.9% of men, hyperplastic adenomas in 32.3% of women and 36.4% of men, tubulovillous adenomas in 10.7% of women and 18.1% of men, with no statistically significant difference between the groups. Villous adenomas were present in 3.6% of men, but no cases were detected in women (Table 2).

Table 2. Distribution of polyps detected between August 2015 and October 2018 by gender

	2015 August-2018 October				2018 November-2019 January			
	Woman		Male		Woman		Male	
	N	%	N	%	N	%	N	%
Tubular	225	41	382	43.7	16	57.1	23	41.9
Tubulovillous	76	13.9	127	14.5	3	10.7	10	18.1
Villous	16	3	20	2.3	0		2	3.6
Hyperplastic	233	42.1	346	39.5	9	32.2	20	36.4

An analysis of pathology reports from colonoscopies conducted between August 2015 and October 2018 revealed mild dysplasia in 15 patients, moderate dysplasia in 11 patients, and severe dysplasia in 9 patients. All cases of mild dysplasia were associated with tubular adenomas. Among

the patients diagnosed with moderate dysplasia, 4 had tubular adenomas, 4 had villous adenomas, and 3 had tubulovillous adenomas. In the group with severe dysplasia, 5 patients presented with tubular adenomas, 3 with tubulovillous adenomas, and 1 with a villous adenoma (Table 3).

Table 3. Dysplastic polyps detected in colonoscopies performed between 2015 August and 2018 October

	2015 August-2018 October			2018 November-2019 January		
	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Mild dysplasia	Moderate dysplasia	Severe dysplasia
Tubular	15	4	5	2	0	0
Villous	0	4	1	0	0	1
Tubulovillosis	0	3	3	0	0	0

Among the 150 patients who underwent colonoscopy between November 2018 and January 2019, dysplasia was identified in three individuals. Of these, two patients had tubular polyps and one had a villous polyp. The number of high-risk polyps identified was 222 in procedures conducted between August 2015 and October 2018, and 14 in the later period from November 2018 to January 2019. The ADR for procedures between August 2015 and October 2018 was 26.4% in female patients and 36% in male patients. During the period from November 2018 to January 2019, the ADR was slightly higher, reaching 27.5% in females and 43% in males.

In terms of sedation, 91.4% of colonoscopies performed between August 2015 and October 2018 involved the use

of sedation. Of these, 95.4% received a combination of an opioid and a benzodiazepine, 3.8% received only an opioid, and 0.8% were administered a benzodiazepine alone. Between November 2018 and January 2019, the sedation rate increased to 98%, with 98.6% of patients receiving the combined opioid-benzodiazepine regimen and 1.4% receiving opioids alone. Pethidine was the opioid of choice, while midazolam was the preferred benzodiazepine.

The overall colorectal cancer detection rate between August 2015 and October 2018 was 4%, with a breakdown of 3.5% in females and 5.3% in males. Similar rates were observed in the period from November 2018 to January 2019, with detection rates of 4% overall, 2.8% in females, and 4.9% in males (Table 4).

Table 4. Number and proportions of patients who received sedation.

	August 2015-October 2018		November 2018-January 2019	
	N	%	N	%
Total patients sedated	2426	91.4	147	98

Among the colorectal cancer cases identified between August 2015 and October 2018, 115 were adenocarcinomas, two were signet ring cell carcinomas, one was non-Hodgkin lymphoma, two were malignant epithelial tumors, and one was diagnosed as a granular cell tumor. Among the patients who underwent colonoscopy between November 2018 and January 2019, five cases of colorectal adenocarcinoma and one case of renal cell carcinoma metastasis were found.

Cecal intubation was successfully achieved in 2179 out of 2654 colonoscopies (82.1%) performed between August 2015 and October 2018, and in 127 out of 150 procedures

(84.6%) conducted between November 2018 and January 2019. When analyzed by sex, the cecal visualization rate for females and males during the earlier period was 81.9% and 82.1%, respectively. In the later period, these rates slightly increased to 84% in females and 85.1% in males. However, no statistically significant differences were observed between the groups ($p>0.05$).

The terminal ileum was visualized in 60.4% of procedures performed between August 2015 and October 2018, compared to 68% of those conducted between November 2018 and January 2019 (Table 5).

Table 5. Gender distribution of colonoscopies conducted between August 2015 and October 2018				
	August 2015-October 2018		November 2018-January 2019	
Total patients with cecum imaging	2179/2654	82%	127/150	84.6%
Female patient undergoing cecum imaging	982/1198	81.9%	58/69	84%
Male patient undergoing cecum imaging	1197/1457	82.1%	69/81	85.1%

In the comparison between premedicated and non-premedicated patients, the cecal intubation rate was 84.5% in the premedicated group, whereas it was 61% in the non-premedicated group, showing a statistically significant difference between the two groups ($p<0.05$) (Table 6).

Table 6. Patients undergoing terminal ileum imaging		
	August 2015-October 2018	November 2018-January 2019
Patients undergoing terminal ileum imaging	1604/2654	102/150

Additionally, the duration of colonoscopy was recorded for procedures performed between 2018 November and 2019 January, with a mean colonoscopy duration of 13.6 minutes.

DISCUSSION

The ADR is defined as the proportion of colonoscopies in which at least one adenomatous lesion is detected (16). An ADR of 20% or more is typically regarded as an acceptable benchmark for colorectal cancer prevention programs (17). The typical reference for ADR is set at 25%, with 30% for men and 20% for women (14). ADR is currently the only quality indicator with a proven direct correlation to colorectal cancer prevention. A 2014 study by Corley et al. involving 314,872 colonoscopies concluded that a 1% increase in ADR led to a 3% decrease in cancer incidence (18). In a separate study with 500 patients, the ADR for standard colonoscopy was found to be 20.7% (19). Coşkun et al. (20) reported 13.3%, Solakoğlu et al. (21) reported the frequency of colorectal polyps as 11.1% in patients over the age of 18 who underwent colonoscopy for various indications, and Şahintürk et al. (22) reported the prevalence of colorectal polyps as 34.9% in a study of 2512 patients. In our study, between August 2015 and October 2018, the ADR was 26.4% in women and 36% in men. Between 2018 November and 2019 January, this increased slightly to 43% in male and 27.5% in females, which aligns with the figures reported in the literature.

Colorectal polyps and tumors are more commonly found in men than in women. In our study, polyps were more frequently found in men during the colonoscopies performed between August 2015 and October 2018, while polyps were more common in women between November 2018 and January 2019. Tubular polyps, which are the most common type of colon polyp (23), were the predominant histopathological finding in our study. Additionally, the polyps we detected were primarily located in the distal colon, which is consistent with existing studies (24).

Patient discomfort during colonoscopy can be alleviated with sedative drugs. There is significant variation in sedation practices across different centers, with some facilities opting not to use sedation, while

others standardize the use of a combination of benzodiazepines and opiates (25). Some studies have reported a significantly higher ADR when colonoscopies were performed under sedation, while others found no significant impact of sedation on ADR (Bannert et al., 2012; Lee et al., 2014; Zhao et al., 2020) (26-28). In our study, the sedation rate was 91.4% between August 2015 and October 2018. When analyzing the difference between premedicated and non-premedicated patients, we found that cecal intubation was achieved in 84.5% of premedicated patients and only 61% of non-premedicated patients. This suggests that premedication may have contributed to a more thorough examination by extending the duration of the procedure (29). Cecal intubation is crucial for visualizing the entire cecum, including the medial wall from the ileocecal valve to the appendix opening (30). Baxter et al. (31) indicated that; lower cecal intubation rates have been linked to an increased incidence of proximal colon cancer (32). Although cecal intubation can be difficult, it is generally agreed that endoscopists should attain a cecal intubation rate of at least 90% across all procedures, and this rate should be $\geq 95\%$ in screening colonoscopies (33). Cecal intubation rates were of 97% or higher in colonoscopy procedures performed on screening patients would have positive effects on the adenoma detection rate in studies conducted in United States (34-36). Cecal and terminal ileum images are important to confirm completion of colonoscopy (37). In our study, however, the cecal intubation rates were lower than the recommended standards, suggesting the need for improvement.

In terms of colorectal cancer detection, Alsumait et al. (38) identified 442 colorectal cancers from 3701 colonoscopies, with a cancer detection rate of 11.9%. Utku et al. found that 6.2% of patients with fecal occult blood had cancer (39). In our study, the overall colorectal cancer detection rate was 4%, with adenocarcinoma being the most common type. This rate might reflect the reasons patients underwent colonoscopy, as cancer detection rates are often influenced by the clinical indications for the procedure. In a 2012 study by Lieberman et al., the American Gastroenterological Association recommended that patients with more than 10 adenomas undergo control colonoscopy within three years

(40). In our study, however, only 2 out of 10 such patients received follow-up colonoscopies, which did not align with the recommended guidelines.

A limitation of our study was the lack of withdrawal time data for colonoscopies performed before November 2018.

CONCLUSION

In conclusion, this study evaluated whether colonoscopic procedures performed at the Endoscopy Unit of the Gastroenterology Clinic, Firat University Hospital, between August 2015 and January 2019 met internationally accepted quality standards. Although the adenoma detection rates in our study aligned with the literature, we observed that both the cecal intubation and colorectal cancer detection rates fell below the recommended standards. This suggests that while recent improvements have been made, further efforts are required to align with optimal practice standards. We believe these findings will offer useful insights for improving colonoscopy procedures in other healthcare institutions.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: Ethical approval of study was obtained on 07.02.2019 (approval number: 07) from Firat University Ethics Committee, and all procedures were carried out in line with the principles set forth in the 2013 revision of the Declaration of Helsinki.

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Psychological Predictors of Addiction Severity in Substance Users: The Roles of Stress, Social Anxiety, and Anxiety Sensitivity

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Abstract

Aim: This study investigated the relationships between social anxiety, anxiety sensitivity, general distress, and addiction severity in individuals undergoing treatment for substance use disorders.

Material and Method: A total of 145 participants diagnosed with substance use disorder were recruited from the Alcohol and Drug Treatment Center (AMATEM) of Ankara Training and Research Hospital.

Results: When examining the results of the current study, anxiety sensitivity and general distress were found to be significantly and positively correlated with addiction severity, whereas social anxiety was not significantly associated. Hierarchical regression analyses revealed that anxiety sensitivity initially predicted addiction severity; however, this effect diminished once general distress was included in the model, underscoring general distress as the stronger and more robust predictor.

Conclusion: These findings suggest that broad emotional distress—encompassing symptoms of depression, anxiety, and stress—may be more influential in driving substance use severity than the specific fear of anxiety-related sensations. The study also discussed theoretical models explaining anxiety sensitivity's role in substance use through moderator and mediator mechanisms, but emphasized that general distress accounted for much of the variance related to addiction severity. Contrary to some previous literature, social anxiety did not contribute significantly, potentially due to the clinical nature of the sample and the treatment-seeking status of participants. The results highlight the importance of addressing transdiagnostic emotional vulnerabilities, particularly general distress, in substance use treatment. Interventions such as emotion regulation training, cognitive-behavioral therapy, and mindfulness-based approaches may be effective in reducing reliance on substances to cope with negative affective states. Overall, the study highlights the need for integrated treatment strategies targeting broad emotional difficulties to mitigate addiction severity.

Keywords: Anxiety sensitivity, social anxiety, distress, substance use disorders

INTRODUCTION

Substance use remains a pervasive global public health concern, inflicting significant detriments on individuals' physical and psychological well-being (1). Among the various psychiatric comorbidities observed in substance-using populations, anxiety disorders—particularly social anxiety disorder (SAD)—are disproportionately represented. Social anxiety, characterized by intense fear of negative evaluation and avoidance of social interactions, has been frequently identified as a catalyst for substance use initiation. Individuals experiencing social discomfort often turn to psychoactive substances, such as alcohol, cannabis, and benzodiazepines, which are perceived to facilitate relaxation and ease social interactions (2,3). These

substances can temporarily attenuate social fears and enhance perceived social competence, thus reinforcing their use in social situations.

However, while substance use may provide short-term relief from social anxiety symptoms, this coping mechanism tends to produce adverse long-term consequences. Persistent reliance on substances to mitigate anxiety can disrupt natural social coping skills, exacerbate interpersonal difficulties, and ultimately lead to social isolation (4). Furthermore, repeated substance use may heighten baseline anxiety and sensitivity to stress, thereby perpetuating and potentially intensifying social anxiety symptoms over time (5). This cyclical relationship underscores the bidirectional and mutually reinforcing nature of social anxiety and substance use disorders.

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In addition to social anxiety, anxiety sensitivity (AS)—defined as the fear of anxiety-related sensations stemming from beliefs about their potential harmful consequences—has emerged as another salient vulnerability factor for substance misuse. Individuals high in anxiety sensitivity are more likely to interpret benign bodily sensations as threatening, which can result in maladaptive efforts to suppress or avoid such experiences (6). Substance use often serves as a readily accessible means to blunt these internal cues, positioning anxiety sensitivity as a potential contributor to both substance use initiation and increase in addiction severity. Prior research suggests that heightened anxiety sensitivity is associated with increased addiction severity and may potentiate the progression toward more entrenched patterns of misuse (7).

Despite growing interest in these psychological risk factors, few studies have simultaneously examined the interconnected roles of social anxiety, anxiety sensitivity, and addiction severity within substance-using populations (8). Moreover, the relative and combined contributions of social anxiety and anxiety sensitivity to addiction severity remain poorly understood (5). Clarifying these relationships is critical to inform the development of targeted interventions designed to address underlying psychological mechanisms that may sustain substance dependence.

Accordingly, the present study aims to investigate the interplay between social anxiety, anxiety sensitivity, and addiction severity among individuals who use substances. Specifically, this research seeks to determine whether elevated levels of social anxiety, anxiety sensitivity, and general distress are associated with increased addiction severity, and whether these factors interact to exacerbate substance use behaviors. By addressing these questions, this study endeavors to advance understanding of the psychological pathways supporting addiction and to inform the design of more effective prevention and intervention strategies.

Based on existing literature, we hypothesize that (H1) social anxiety will be positively associated with addiction severity, (H2) anxiety sensitivity will be positively associated with addiction severity, and (H3) general distress will be positively associated with addiction severity. Furthermore, we hypothesize that (H4) anxiety sensitivity, social anxiety, and general distress will significantly predict addiction severity.

MATERIAL AND METHOD

Study Sample

A total of 145 individuals diagnosed with substance use disorders were recruited for this study. All participants were receiving treatment at an Alcohol and Drug Treatment Center (ADTC-AMATEM). Inclusion criteria required participants to be aged 18 years or older and to meet the diagnostic criteria for substance use disorder according to standardized clinical assessments conducted at the center. Individuals with severe cognitive impairment or active psychotic symptoms that could

interfere with the completion of self-report measures were excluded from participation.

Prior to data collection, all participants were provided with detailed information about the aims and procedures of the study and gave written informed consent in accordance with ethical guidelines. The study protocol was approved by the Ankara Training and Research Hospital ethics committee (decision date and number: 17.04.2025, E-25-479), ensuring compliance with the principles outlined in the Declaration of Helsinki. Data were collected through face-to-face interviews and self-administered questionnaires in a private setting within the treatment center to ensure confidentiality and minimize potential biases. Participation was entirely voluntary, and individuals were assured that their treatment would not be affected by their decision to participate or withdraw from the study.

Measures

In the present study, data were collected using one sociodemographic form and four self-report scales designed to assess psychological symptoms and substance use patterns. These instruments are detailed below.

Sociodemographic Data Form: A sociodemographic form, developed by the researchers, was administered to gather relevant personal and clinical information. This form included questions related to participants' age, gender, educational level, employment status, age at initiation of substance use, type of substance first used, and history of psychiatric and substance-related problems.

Depression Anxiety Stress Scales-21 (DASS-21): The DASS-21 is the short form of the original 42-item scale developed by Lovibond and Lovibond (1995) to assess symptoms of depression, anxiety, and stress (9). The Turkish adaptation and validation of the scale were performed by Yılmaz et al. (2017) (10). The DASS-21 consists of 21 items divided equally into three subscales: depression (items 3, 5, 10, 13, 16, 17, 21), anxiety (items 2, 4, 7, 9, 15, 19, 20), and stress (items 1, 6, 8, 11, 12, 14, 18). Items are rated on a 4-point Likert scale, with higher scores reflecting greater symptom severity. The internal consistency (Cronbach's alpha) was found to be .67 for depression, .86 for anxiety, .67 for stress, and .87 for the total scale, indicating satisfactory reliability.

Anxiety Sensitivity Index (ASI): The Anxiety Sensitivity Index (ASI), originally developed by Reiss et al., is a widely used self-report instrument designed to assess the extent to which individuals fear anxiety-related sensations (11). The scale conceptualizes anxiety sensitivity as the tendency to interpret such sensations—such as palpitations, shortness of breath, and cognitive disruptions—as harmful or dangerous. The ASI consists of 16 items, each rated on a 5-point Likert scale ranging from 0 (very little) to 4 (very much). Higher scores reflect greater anxiety sensitivity, which is considered a risk factor for the development and maintenance of various anxiety disorders as well as substance use behaviors. The Turkish adaptation of the ASI was conducted by Ayvaşık (2000), demonstrating satisfactory psychometric properties (12).

Liebowitz Social Anxiety Scale (LSAS): The LSAS, developed by Liebowitz, is a widely used instrument designed to assess fear and avoidance in social and performance situations. This self-report scale consists of 48 items, divided equally between fear/anxiety and avoidance dimensions. Participants rate each item on a 4-point Likert scale. The Turkish adaptation and validation were conducted by Soykan et al., confirming the scale’s validity and reliability in Turkish samples.

Drug Use Disorder Identification Test (DUDIT): The DUDIT is an 11-item screening tool that evaluates the frequency of substance use, substance-related problems, and dependence symptoms over the past year (13). It offers practical advantages, including brevity and multiple response options. Scores of 2 or higher for women and 6 or higher for men suggest problematic use, while scores of 25 or above indicate high-risk use. The Turkish version has been validated for use in various populations, including incarcerated individuals and those using heroin (14,15).

Statistical Analyses

Data Analysis Plan

Prior to conducting the primary analyses, several preliminary steps were taken to verify that the core assumptions of the study were satisfied. As part of this

process, the internal consistency of the measurement tools was assessed using Cronbach’s alpha coefficients, inter-variable correlations were analyzed, and the normality of the data distribution was examined through skewness and kurtosis statistics. To determine whether the data met the assumption of normality, the absolute values of these indicators were reviewed in light of the widely accepted threshold of ± 2 , which is regarded as an acceptable deviation range in the literature (16). Subsequently, Pearson correlation analysis was run to assess the associations between the main study variables.

In the final stage, the study’s central hypothesis was tested through a hierarchical multiple regression analysis. Specifically, a stepwise approach was followed, in which the examination of the incremental predictive power of each set of variables starting from demographic variables toward social anxiety, anxiety sensitivity, and general distress was tested on addiction severity (The DASS-21 total score was considered a measure of general distress and served as a variable in the analyses). All these mentioned analyses were conducted by using SPSS version 27.

RESULTS

First, the results of frequency analyses are presented in Table 1.

Table 1. Frequency analysis results				
Variable	Group	Frequency	% of Total	Cumulative %
Gender	Female	3	2.1	2.1
	Male	142	97.9	100
House income	“0-20k”	61	42.1	42.1
	“21k-50k”	66	45.5	87.6
	“51k-100k”	18	12.4	100
Marital status	Married	47	32.4	32.4
	Single	98	67.6	100
Employment status	Yes	116	80	80
	No	29	20	100
Housing status	Permanent	135	93.1	93.1
	Temporal	10	6.9	100
Medication use by substance type	Met use	4	2.8	2.8
	Heroin use	136	93.8	96.6
	Other	5	3.4	100
Current substance use	Yes	12	8.3	8.3
	No	133	91.7	100
Current type of substance in usage	None	132	91	91
	Heroin	8	5.5	96.6
	Met	4	2.8	99.3
	Pregabaline	1	0.7	100
Iv substance use	No	120	82.8	82.8
	Yes	25	17.2	100
History of iv substance use	Yes	7	4.8	4.8
	No	138	95.2	100
Type of first substance used	Marijuana	98	67.6	67.6
	SC	2	1.4	69
	Ecstasy	2	1.4	70.3
	Heroin	42	29	99.3
	Pregabaline	1	0.7	100

Note: IV: intravenous; met: methamphetamine; SC: Synthetic cannabinoids

Table 1. Frequency analysis results				
Variable	Group	Frequency	% of Total	Cumulative %
Way of first substance used	Aspiration	131	90.3	90.3
	Eat	5	3.4	93.7
	Swallow/Pill	4	2.8	96.6
	IV Injection	5	3.4	100
Polydrug use	Yes	47	32.4	32.4
	No	98	67.6	100
Family history of substance use	Yes	5	3.4	3.4
	No	140	96.6	100
History of suicide	Yes	17	11.7	11.7
	No	126	86.9	98.6
	Unknown	2	1.4	100

Note: IV: intravenous; met: methamphetamine; SC: Synthetic cannabinoids

Preliminary Analyses

Prior to testing the primary hypotheses, preliminary analyses were conducted on the study variables, including data screening, descriptive statistics, evaluation of internal consistency, assessment of normality, and examination of intervariable correlations. The dataset was checked for outliers and missing values; only one

missing value was found for the social anxiety total score, which was not considered problematic. Skewness values ranged from .162 to 1.267 and kurtosis values from -.642 to 1.757, indicating an approximately normal distribution. Cronbach’s alpha coefficients ranged from .89 to .96, demonstrating high internal consistency. Descriptive results are presented in Table 2.

Table 2. Descriptive statistics						
Variables	N	Mean	SD	Skewness	Kurtosis	α
Age	145	33.93	6.63			
Education (years)	145	10.48	2.67			
Anxiety sensitivity	145	25.12	12.93	.162	-.804	.89
Social anxiety	144	48.36	16.56	.941	1.757	.96
General distress	145	19.89	15.72	.485	-.642	.96
Addiction severity	145	8.86	9.91	1.267	1.189	.90

Following the descriptive statistics, Pearson correlation analysis was conducted to see the correlations between the main study variables. Considering the results, addiction severity was significantly and positively correlated with both anxiety sensitivity ($r=.33$, $p<.001$) and general distress ($r=.47$, $p<.001$), but not with social anxiety ($p>.05$). Additionally, a moderate significant association was captured between anxiety sensitivity and general distress ($r=.53$, $p<.001$). Finally, social anxiety was only significantly associated with general distress ($r=.29$, $p<.001$), but not with the remaining variables ($p>.05$). All these correlational findings were displayed under Table 3 below.

Table 3. Correlations among the study variables				
	1	2	3	4
1. Anxiety sensitivity	—			
2. Social anxiety	.13	—		
3. General distress	.53*	.29*	—	
4. Addiction severity	.33*	.05	.47*	—

* $p<.001$

Hierarchical Regression Analysis

To investigate the predictors of addiction severity, a hierarchical regression analysis was conducted. In the first step, basic demographic variables of age, gender, marital status, income, and years of education were entered into the model. In the second step, social

anxiety was added. In the third and fourth steps, anxiety sensitivity and general distress were entered sequentially. This stepwise approach allowed for the examination of the incremental predictive power of each set of variables, progressing from basic demographics to more specific psychological factors.

Before proceeding with the analysis, the assumptions required for regression analysis—namely normality, linearity, multicollinearity, and homoscedasticity (equal variance)—were examined. For normality, in addition to the histogram plot, the skewness and kurtosis values reported above were within acceptable limits (i.e., $<|2|$), and thus the assumption of normality was considered to be met. Multicollinearity was assessed by examining correlations between variables as well as Tolerance and Variance Inflation Factor (VIF) values. Since all values were below the cutoff value of 2 (ranging from .649 to 1.541), no multicollinearity issues were observed. The assumption of homoscedasticity was evaluated through the inspection of the scatterplot of residuals, which did not indicate any violation of this assumption. Lastly, to determine whether there were any influential outliers in the dataset, Cook’s Distance values were calculated; since all values were below 1, no violations were detected in this regard either. Based on these findings, multiple regression analysis was conducted as all assumptions were met.

Moving to the results, in Step 1, the model itself was not significant, $F(5, 143)=.199$, $p=.962$, accounted for less than 1% of variance in addiction severity, $R^2=.007$. In the Step 2, the addition of social anxiety also did not make a significant difference in addiction severity, $F(6, 143)=.226$, $p=.548$, explaining 1% of variance in addiction severity, $R^2=.01$.

In the third step, the addition of anxiety sensitivity made the model statistically significant, $F(7, 143)=2.445$, $p=.000$, resulting in 11% of variance explained in addiction severity, $R^2=.11$. Anxiety sensitivity ($\beta=.33$, $p=.000$) was a significant predictor, whereas social anxiety ($\beta=.02$, $p=.412$) was not

along with demographic variables ($p>.05$).

In Step 4, the addition of general distress led to a further improvement in model fit, $F(8, 143)=5.69$, $p<.001$, with the model explaining 25% of the variance in addiction severity ($R^2=.25$). At this stage, only general distress significantly predicted addiction severity ($\beta=.47$, $p<.001$), while the previously significant effect of anxiety sensitivity was no longer statistically significant. This suggests that general distress accounted for much of the variance initially explained by anxiety sensitivity. The results were displayed under Table 4.

Table 4. Hierarchical regression analysis results					
	B	β	t	p	R2
Model 1					.007
Age	-.07	-.05	-.585	.559	
Gender	.61	.01	.102	.919	
Marital status	-.98	-.05	-.526	.600	
Income	-.65	-.04	-.507	.613	
Year of education	-.09	-.02	-.284	.777	
Model 2					.010
Age	-.08	-.06	-.643	.521	
Gender	.18	.00	.030	.976	
Marital status	-.71	-.03	-.368	.713	
Income	-.72	-.05	-.560	.577	
Year of education	-.07	-.02	-.213	.831	
Social anxiety	.03	.05	.602	.548	
Model 3					.112
Age	-.05	-.03	-.397	.692	
Gender	1.03	.02	.182	.856	
Marital status	-1.12	-.05	-.643	.521	
Income	-.18	-.01	-.149	.882	
Year of education	.06	.02	.200	.842	
Social anxiety	.00	.00	.025	.980	
Anxiety sensitivity	.25	.33	3.952	.000	
Model 4					.252
Age	-.10	-.07	-.877	.382	
Gender	-1.832	-.03	-.346	.730	
Marital status	-1.474	-.07	-.876	.382	
Income	.488	.03	.424	.672	
Year of education	-.01	.00	-.014	.989	
Social anxiety	-.06	-.10	-1.161	.248	
Anxiety sensitivity	.07	.10	1.064	.289	
General distress	.30	.47	5.033	.000	

DISCUSSION

The present study aimed to explore the associations between social anxiety, anxiety sensitivity, and addiction severity in a clinical sample of individuals diagnosed with substance use disorders. The results revealed that while both anxiety sensitivity and general distress were significantly correlated with addiction severity, social anxiety did not show a significant association. Furthermore, in the hierarchical regression analysis, anxiety sensitivity initially emerged as a significant predictor of addiction severity; however, this effect was

no longer significant when general distress was added to the model. Ultimately, only general distress significantly predicted addiction severity, accounting for the largest proportion of explained variance.

These findings contribute to the growing body of literature emphasizing the critical role of transdiagnostic emotional vulnerability factors—such as general distress and anxiety sensitivity—in the development and maintenance of substance use disorders. Consistent with previous research, heightened anxiety sensitivity was associated with greater addiction severity, suggesting

that individuals who interpret anxiety-related sensations as dangerous may be more likely to engage in substance use as a maladaptive coping strategy (5).

Several theoretical models have been proposed to explain the relationship between anxiety sensitivity (AS) and addiction severity, with particular emphasis on moderator and mediator frameworks (17). In moderator models, AS is thought to influence the strength or direction of the association between anxiety and substance use. For instance, individuals with high AS may exhibit greater avoidance motivation in response to anxiety or anxiety-related expectancies, leading them to use substances such as alcohol or drugs more readily as a coping mechanism. Conversely, mediator models suggest that AS plays a more mechanistic role, explaining how individuals come to use substances to manage anxiety. Specifically, those with elevated AS may be more likely to perceive anxiety-related sensations as intolerable or dangerous, which increases their motivation to reduce these sensations through substance use. This negative reinforcement process, in turn, may contribute to higher addiction severity over time. These conceptual models have been supported by empirical findings (18-20), emphasizing the relevance of AS in understanding individual differences in substance use behaviors and the development of addiction. In our study, the predictive role of anxiety sensitivity was diminished once general distress was accounted for, indicating that the broader experience of negative affect may be a more salient factor in substance use severity than the specific fear of anxiety-related sensations. General distress may influence substance use through multiple pathways. A five-year longitudinal study found that individuals with above-average levels of psychological distress were more likely to engage in substance use over time (21). In another study, total scores on the DASS-21 were found to mediate the relationship between emotion dysregulation and drug craving (22).

Contrary to expectations, social anxiety was not significantly associated with addiction severity in either the correlation or regression analyses. This finding diverges from some prior studies that have linked social anxiety symptoms to problematic substance use. A systematic review found that shyness and social anxiety in adolescents are associated with decreased use of tobacco, alcohol, and cannabis/substances, whereas social anxiety disorder is linked to increased substance use (23). One possible explanation for this discrepancy lies in the clinical characteristics of the present sample. The participants were already engaged in treatment for substance use disorders, and their current substance use patterns may be more strongly influenced by generalized psychological distress than by social-specific fears. Additionally, social anxiety may exert more influence in the early stages of substance use initiation rather than in the maintenance phase captured in this treatment-seeking sample.

The hierarchical structure of the regression analysis provided further insight into the relative contribution of psychological factors. The finding that general distress accounted for a substantial portion of the variance in addiction severity underscores its central role as a broad transdiagnostic factor. General distress, which encompasses symptoms of depression, anxiety, and stress, likely represents a cumulative emotional burden that drives individuals toward substance use as a form of emotional regulation. These results align with affect regulation models of addiction, which posit that substances are frequently used to manage aversive emotional states (24).

From a clinical perspective, these findings underscore the importance of assessing and addressing general emotional distress in substance use treatment programs. Interventions such as emotion regulation training, cognitive-behavioral therapy, and mindfulness-based approaches may be particularly beneficial in reducing the reliance on substances to cope with negative affective states (25,26). Furthermore, while anxiety sensitivity may not independently predict addiction severity beyond general distress, its inclusion in screening tools could still be valuable for identifying individuals who may be more vulnerable to escalating use in response to internal distress cues.

Despite its contributions, this study is not without limitations. First, the cross-sectional design precludes causal interpretations regarding the directionality of relationships among the study variables. Longitudinal studies are needed to elucidate whether anxiety sensitivity or general distress temporally precedes increases in substance use severity. Second, all data were self-reported, which may introduce response biases or inaccuracies. Third, the generalizability of the findings may be limited to treatment-seeking individuals, and the role of social anxiety in non-clinical or early-stage substance users warrants further investigation. Additionally, the homogeneity of the treatment-seeking sample may limit variability, potentially affecting the detection of certain associations. Furthermore, the absence of data on psychiatric comorbidities restricts the ability to examine how these factors might moderate or mediate the observed relationships. Addressing these confounders in future research could provide a more nuanced understanding of the mechanisms underlying addiction severity.

Future research should consider incorporating behavioral or physiological measures of emotional reactivity and regulation to complement self-report data. Additionally, examining potential mediating or moderating variables—such as coping styles, trauma history, or impulsivity—may provide a more nuanced understanding of how anxiety-related constructs influence substance use trajectories. Specifically, future studies could investigate whether specific emotion regulation difficulties or trauma

history serve as mediators between general distress and addiction severity. It would also be valuable to explore whether similar patterns are observed in non-treatment-seeking or adolescent populations. Moreover, research could examine if interventions specifically targeting anxiety sensitivity produce indirect effects on distress levels and substance use outcomes over time.

CONCLUSION

In conclusion, the present study highlights the differential roles of anxiety sensitivity and general distress in predicting addiction severity among individuals with substance use disorders. While social anxiety did not emerge as a significant factor, the strong association between general distress and substance use severity underscores the need for integrated treatment approaches that target broad emotional vulnerabilities. By refining our understanding of the psychological mechanisms underlying substance dependence, such efforts may ultimately enhance the effectiveness of intervention strategies.

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Investigation of Material Effects in Knee Prosthesis Design Using Finite Element Method

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Abstract

Aim: Total knee arthroplasty (TKA) is an effective orthopedic intervention for patients experiencing significant pain and reduced mobility due to advanced joint degeneration. One of the most critical determinants of TKA success is the mechanical and biological properties of the implant materials used. The Finite Element Method (FEM) serves as a powerful engineering tool for modeling and analyzing the mechanical behavior of prosthetic components in detail. This study aimed to investigate the mechanical effects of different material combinations used in knee prosthesis design through FEM analyses.

Material and Method: The mechanical behavior of three commonly used material combinations in knee prostheses—CoCr–UHMWPE, Ti–UHMWPE, and CoCr–Ti—was comparatively analyzed using the Finite Element Method (FEM). The geometry used in the FEM analysis was based on an anatomical knee model derived from computed tomography (CT) data. The 3D geometry was imported into ANSYS Mechanical APDL software, and adaptive meshing was applied to critical regions such as the femur–tibia contact area. The resulting models consisted of approximately 150,000 to 300,000 elements.

Results: Combinations containing CoCr exhibit lower stress concentrations. The Ti–UHMWPE combination exhibits the highest deformation at 0.93 mm, while the CoCr–Ti combination presents the lowest displacement, reflecting its higher structural rigidity. The comparison between three materials indicates that the CoCr–UHMWPE combination offers the most balanced performance in terms of stress distribution, deformation, and contact pressure.

Conclusion: The central finding of this study is that the CoCr–UHMWPE combination may represent the most optimal structure in terms of mechanical load distribution, contact stability, and deformation control in knee prosthesis applications. Although the Ti–UHMWPE configuration provides flexibility advantages, it must be cautiously evaluated for long-term structural stability. The CoCr–Ti configuration, while highly rigid, was shown to carry a potential risk of local stress-induced micro-damage.

Keywords: Total knee arthroplasty, finite element method, knee prosthesis

INTRODUCTION

Total knee arthroplasty (TKA) is an effective orthopedic intervention for patients experiencing significant pain and reduced mobility due to advanced joint degeneration. In recent years, there has been a notable increase in the number of TKA procedures performed worldwide, driven by an aging population, rising obesity rates, and a growing demand for active lifestyles (1).

One of the most critical determinants of TKA success is the mechanical and biological properties of the implant materials used. Parameters such as elastic modulus, stiffness, fatigue resistance, and biocompatibility have a

direct impact on implant stability in the short term, as well as on long-term risks such as wear and loosening (2).

The most commonly used materials in knee prostheses include cobalt-chromium alloy (CoCr), titanium alloy (Ti-6Al-4V), and ultra-high-molecular-weight polyethylene (UHMWPE). Each of these materials offers unique advantages and limitations in terms of load distribution, contact pressure, and wear resistance (3).

At this point, the Finite Element Method (FEM) serves as a powerful engineering tool for modeling and analyzing the mechanical behavior of prosthetic components in detail. FEM enables precise evaluation of contact surfaces,

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stress concentrations, and deformation regions. These analyses provide critical insights into prosthesis design and material selection (4).

In this study, the mechanical effects of different material combinations used in knee prosthesis design are investigated through FEM analyses. The study evaluates how material selection affects load transmission, contact pressures, and long-term performance (5).

MATERIAL AND METHOD

In this study, the mechanical behavior of three commonly used material combinations in knee prostheses—CoCr–UHMWPE, Ti–UHMWPE, and CoCr–Ti—was comparatively analyzed using the FEM. The aim was to investigate the effects of these materials on contact pressure, stress distribution, and deformation characteristics (1). Since this study is based on FEM simulations and does not involve human or animal subjects, ethical approval was not required.

Prosthesis Model and Geometry Development

The geometry of the knee prosthesis used in the analysis was based on a high-resolution anatomical knee structure obtained from computed tomography (CT) data. Based on the bone morphology of the real human knee, the femur and tibia bones were carefully isolated and segmented in the axial plane. The volumetric data was transferred to the CAD modeling software SolidWorks, where the femoral and tibial components were reconstructed in accordance with the clinical implant dimensions and anatomy. During modeling, the focus of the analysis was on load-bearing behavior; therefore, soft tissue components such as the meniscus, anterior cruciate ligament (ACL), posterior cruciate ligament (PCL) and collateral ligaments were excluded. This approach allowed the load transfer and contact mechanics analyses to be evaluated more clearly. This parametric model was optimized for both dimensional accuracy and suitability for numerical analysis (6).

Meshing and Numerical Modeling

The obtained three-dimensional CAD models were transferred to the ANSYS Mechanical APDL software environment, where finite element analyses were carried out. In order to achieve high accuracy in numerical analysis, an adaptive meshing strategy was applied, especially in critical areas with high stress and deformation potential, such as the femur-tibia contact zone. In these areas, element sizes were reduced to a minimum of 0.5 mm, and edge density was increased to improve the accuracy of contact mechanics and stress analysis results. In regions of the model that are considered less critical, a sparser mesh structure was preferred to optimize the computation time and make efficient use of system resources (Figure 1).

As a result, the resulting finite element models are structured to contain approximately 150,000 to 300,000 three-dimensional elements. This mesh structure allows both high-resolution regional analysis and numerically accurate modeling of global loading conditions. In addition,

element types and shape functions were determined in accordance with the type of analysis, and nonlinear contact definitions and convergence control were provided in contact areas (3).

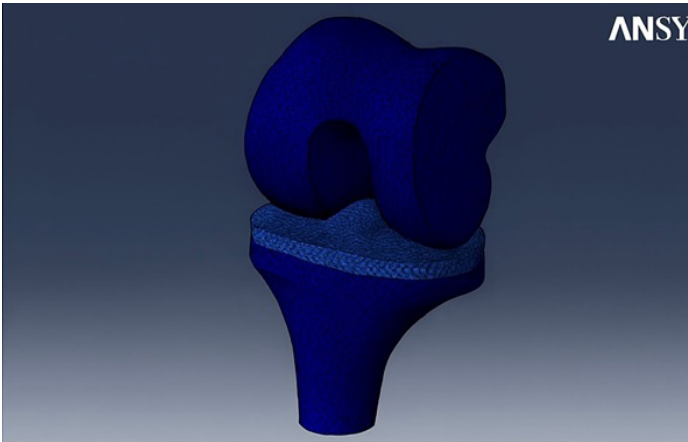


Figure 1. Meshing and numerical modeling

Material Properties

All materials used are modeled as isotropic and linear elastic. Mechanics All material models used in this study are defined assuming isotropic and linear elastic behavior, as is commonly preferred in finite element analysis. This approach provides an acceptable level of structural accuracy along with computational efficiency. The modulus of elasticity (E) and Poisson's ratio (ν) of each material are presented in Table 1 below:

Table 1. Elastic Modulus (E) and son's Ratio (ν) of the materials		
Material	Elastic Modulus (E)	Poisson's Ratio (ν)
CoCr Alloy	210 GPa	0.30
Ti-6Al-4V	110 GPa	0.33
UHMWPE	1.0 GPa	0.46

CoCr was preferred for load-bearing components that require rigidity due to its high elastic modulus. Ti-6Al-4V alloy stands out with its relatively lower stiffness and high biocompatibility, which offers an advantage in terms of deformation tolerance, especially in young and active patient groups.

UHMWPE was used as the tibial femur interface component and assumed a load absorbing role at the contact surfaces with its high energy absorbing capacity. In addition, the time-dependent creep behavior of this material was included in the FEM analysis with the definition of viscoelastic material to improve model accuracy. In this way, the long-term deformation trends of the polymer layer were reflected more realistically (2).

Loading and Boundary Conditions

In the finite element analysis, the loading conditions applied to the knee prosthesis system were structured to model the scenario closest to physiological reality. Accordingly, the loading condition was defined to represent a one-legged stance and a vertical force in the range of approximately 1800-2100 N was applied. This value is based on load-

bearing scenarios assumed to be approximately 2.5-3.0 times body weight and represents the most critical loading phase of the clinical gait cycle.

In the model, the proximal surface of the femur is fully anchored with a fixed boundary condition (fixed support). In this way, load transfer is aimed to be achieved only through the tibial component. The tibial component is free-fitted from its lower surface to a rigid and frictionless plane, thus creating a contact situation similar to natural load transfer.

Nonlinear frictional contact interaction is defined on the contact surfaces between the two components. Accordingly, the contact behavior was modeled with the penalty method in FEM analysis and the friction coefficient $\mu=0.04$ was assigned to improve the physical accuracy of the contact. This value was determined based on the average friction coefficients of metal-polymer interfacial contacts reported in the literature (7).

This modeling approach provided accurate and precise determination of both contact pressure and stress-strain distribution, allowing for a more realistic analysis of the behavior of prosthetic components under clinical loading scenarios.

Evaluation of Output Parameters

In this study, the analyses performed on the finite element model of each material combination were evaluated with respect to structural parameters that are considered clinically critical. The output parameters analyzed include the following criteria, which play a decisive role in terms of both load-bearing capacity and long-term implant stability:

- **Von Mises stress values:** The maximum and average Von Mises stresses were evaluated to analyze the distribution of structural stiffness and stress concentration zones. In particular, these values were used to identify potential microcrack initiation zones.
- **Maximum contact pressure and contact area:** The maximum pressure values and the width of the contact areas on the load transmission surfaces between two prosthetic components were analyzed for wear tendency and risk of superficial damage. The width of the surface area was considered as a parameter that directly affects the homogeneity of the load distribution.

- **Tibial component deformation:** The maximum displacement of the tibial component under applied load was evaluated in terms of structural stability and compatibility of the implant. High deformation indicates a potential risk of loosening and micro-wear.
- **Displacement and creep potential in the UHMWPE layer:** In particular, the time-dependent deformation behavior of the UHMWPE layer, represented by viscoelastic modeling, was investigated; short-term elastic displacement as well as long-term creep tendency were included in the evaluation.

All analyses were carried out separately for each material combination and the results were interpreted visually and numerically in detail for the load carrying behavior, stress concentrations and deformation zones. In this way, the advantages and potential limitations of each combination are presented comparatively (4).

RESULTS

In this study, the mechanical effects of different material combinations used in knee prostheses were evaluated using Finite Element Analysis (FEM). The outputs obtained were analyzed in terms of stress distribution, contact pressure, displacement magnitude, and deformation profiles. Each parameter was interpreted in relation to the biomechanical performance of the respective material.

Analysis and Interpretation

The results of the stress analysis revealed that the material combinations showed significant differences in terms of mechanical compliance levels. The CoCr-UHMWPE combination showed the lowest levels of both maximum (22.1 MPa) and average (15.4 MPa) Von Mises stress values. The homogeneous stress distribution observed in this combination ensures a more even distribution of the load on the contact surface and prevents stress concentrations.

In contrast, the Ti-UHMWPE and CoCr-Ti combinations showed localized stress accumulation, especially in the contact zones, due to the effect of elastic modulus differences. Ti-UHMWPE produced a more diffuse but irregular stress distribution due to its lower modulus of elasticity, while the high stiffness contrast in the CoCr-Ti combination led to superficial but dense stress concentrations (Table 2).

Table 2. von mises stress distribution according to material combinations			
Material combination	Max. von mises stress (MPa)	Average stress (MPa)	Stress distribution property
CoCr–UHMWPE	22.1	15.4	Homogenous, low density
Ti–UHMWPE	25.3	17.2	Widespread, high local stress zones
CoCr–Ti	27.5	18.1	Superficial, localized stress accumulation

These results show that the tensile performance of prosthetic components is closely related not only to the stiffness of the material used but also to the elastic compatibility between the two materials (3).

Analysis and Interpretation

Considering the contact and deformation parameters, the CoCr-UHMWPE combination stands out for having the largest contact area (112 mm²) and one of the lowest

contact pressures (22.1 MPa). This structure allows the load to be distributed over a larger area and homogeneously over the prosthesis contact surface, reducing the risk of superficial wear and local stress concentration.

In contrast, the Ti-UHMWPE combination showed a high deformation tendency (0.93 mm) due to the low elastic modulus. This is considered a disadvantage that may lead to long-term degradation of the UHMWPE layer under dynamic loading, such as creep and permanent deformation.

Although the CoCr-Ti combination has the lowest displacement value (0.66 mm), it carries the risk of stress accumulation and micro-wear on the surface due to the high contact pressure (27.5 MPa) and limited contact area (94 mm²). This shows that rigid structures can increase stress concentration while limiting deformation (1,4).

In conclusion, contact and deformation parameters are important determinants of clinical longevity and mechanical durability, and material selection should be made in favor of combinations that optimize these parameters (Table 3).

Table 3. Contact area, pressure and deformation comparison				
Material combination	Max. contact pressure (MPa)	Contact area (mm ²)	Max. displacement (mm)	Interpretation
CoCr-UHMWPE	22.1	112	0.71	Moderate level, stable
Ti-UHMWPE	25.3	98	0.93	High and elastic deformation
CoCr-Ti	27.5	94	0.66	Lowest deformation, rigid structure

Analysis and Interpretation

Qualitative evaluation of the clinical performance shows that the CoCr-UHMWPE combination exhibits a superior profile in overall stability. This combination offers a prosthetic structure that can provide long-term success, especially in middle-aged and active patients, thanks to the balanced combination of wear resistance, homogeneity of load distribution, and structural stability.

On the other hand, although the Ti-UHMWPE combination offers increased flexibility due to its lower elastic modulus, this feature may lead to decreased

structural stability and increased deformation tendency. Therefore, it is recommended to use this combination in young individuals with light body mass, with careful patient selection.

The CoCr-Ti combination, on the other hand, has the highest structural rigidity and, when combined with high wear resistance, may be preferred, especially in patients exposed to high physiologic loads. However, this combination needs to be carefully evaluated due to its limited load distribution and potential stress accumulation (Table 4).

Table 4. Qualitative evaluation in terms of clinical performance				
Material combination	Abrasion resistance	Load distribution	Structural stability	Clinical suitability profile
CoCr-UHMWPE	High	Balanced	Good	Optimal choice for middle-aged and active individuals
Ti-UHMWPE	Medium	Medium	Low	Cautious use recommended for young and mobile individuals with light body mass
CoCr-Ti	High	Low	Very high	Preferable in cases requiring high structural rigidity

This qualitative analysis aims to holistically evaluate not only biomechanical data but also factors that directly influence clinical decisions, such as patient profile, functional expectations, and implant longevity (6,7).

DISCUSSION

In this study, the biomechanical behavior of three different material pairs, namely CoCr-UHMWPE, Ti-UHMWPE, and CoCr-Ti, in knee prostheses was comparatively analyzed using the FEM. The numerical analyses revealed that the material combination plays an important role not only in structural strength but also in mechanical parameters such as contact pressure distribution, Von Mises stress profile, and deformation capacity, which directly affect the functional performance of the prosthesis (1,3,8).

Interpretation of Mechanical Performance

The interaction of mechanical parameters is considered to be an important factor directly affecting clinical performance. The CoCr-UHMWPE combination, with its

rigidity and energy-absorbing character, allows the load to spread over a wider surface, thus creating homogeneous stress distribution in the contact area and reducing the potential for wear (3,6,9). This structure has the potential to offer long-term structural stability, especially for prostheses subjected to high repetitive loading in the knee joint.

On the other hand, the high deformation (0.93 mm) observed in the Ti-UHMWPE combination, although offering the advantage of flexibility in the short term, should be carefully evaluated as it may cause mechanical deterioration such as creep and microscopic crack formation in the UHMWPE layer in the long term (2,9,10). Although the biocompatible nature of titanium offers a favorable feature, especially in young and active patients, mechanical imbalances may increase the possibility of revision.

Although the CoCr-Ti combination maintains structural rigidity thanks to its low deformation tendency, its high contact pressure (27.5 MPa) and limited contact area

(94 mm²) create localized stress accumulation on the surface, which increases the risk of superficial wear and loosening at the implant-bone interface (4,11). As reported in the literature, such combinations are more susceptible to micro-abrasions during prolonged use under overload.

Therefore, material selection should be based not only on mechanical performance criteria but also on patient profile, activity level, and long-term clinical expectations. The interaction between the stress distribution and deformation profile of material combinations is critical to prolonging prosthesis life and reducing the risk of complications.

Consistency with Literature and Clinical Implications

The findings obtained in this study are highly consistent with the existing literature and confirm the decisive influence of material selection in knee prosthesis design on biomechanical performance. It has been emphasized in various studies that parameters such as stress accumulation, deformation and contact area observed by FEM analyses play a critical role in implant life and clinical stability.

Loi et al. showed that local stress concentrations may adversely affect implant performance and cause microfracture and loosening in their analyses performed with individual-specific FEM models (12). Similarly, Arab et al. stated that mechanical imbalances that may occur at the prosthesis-bone interface in high contact pressure situations threaten long-term implant stability (13).

Maiti and Kumar numerically investigated the deformation and wear trends in the contact zones of CoCr and Ti alloys with UHMWPE under cyclic loading scenarios and analyzed in detail the effects of different combinations on load transfer (8). These results are in direct agreement with the deformation levels observed in our study.

Bhandarkar and Dhatrik reported that the structural stiffness of Ti-6Al-4V alloy may lead to a high risk of deformation if not optimized together with the implant geometry (10). This suggests that titanium-based components should be carefully selected, especially in young and active patient groups. Furthermore, Kang et al. emphasized that the type of tibial insert material directly affects the contact pressure distribution and is an important parameter for prosthesis fit (14).

Finally, the inclusion of the viscoelastic behavior of the UHMWPE layer in FEM analyses provides the opportunity to model the permanent shape changes that occur over time in a more realistic way and increases the accuracy of predictions related to prosthesis life (2,4). This approach allows evaluation of not only the immediate mechanical response but also the long-term biomechanical stability.

Limitations and Future Directions

This study was conducted using the finite element method to comparatively evaluate the biomechanical performance

of different prosthetic materials used in hip arthroplasty. However, some limitations inherent to the nature of the model should be taken into consideration.

Firstly, our analyses were conducted under static loading conditions. In real life, the forces applied to the joint have a dynamic structure that changes over time and includes multi-axial components. Therefore, the loading scenario used in the model does not fully represent all mechanical loads in daily life. In future studies, more complex models that simulate dynamic and multi-axial forces are planned to be included.

Secondly, soft tissue structures (ligaments, capsule, muscle forces, etc.) were not included in this study. It is known that these structures make significant contributions to joint stability and load transfer. Factors that directly affect prosthesis design, such as whether the ACL is preserved or not, have not been evaluated in this context. However, detailed soft tissue modeling that includes such parameters should be addressed in greater depth in a separate study.

Additionally, the fact that different liner or insert designs were not comparatively evaluated in this study can be considered another limitation, particularly in terms of changes in contact stresses. In deformation-sensitive materials such as UHMWPE, the effect of insert geometry and thickness on prosthesis performance is significant, and this topic constitutes an important focus for future studies.

Finally, this study modeled only a single loading position (e.g., single-leg stance). However, different joint positions encountered in daily life, such as squatting or climbing stairs, may also have significant biomechanical effects on the prosthesis. Integrating these scenarios into future models would further enhance the clinical validity of the results.

All these issues should be carefully considered when interpreting the study. However, these limitations do not invalidate the main objective of the current study or the comparative results it presents. The relevant points are planned to be addressed in detail in advanced studies involving more comprehensive and dynamic modeling.

CONCLUSION

This study comparatively analyzed the biomechanical performance of three different material combinations commonly used in total knee arthroplasty-CoCr-UHMWPE, Ti-UHMWPE and CoCr-Ti-using the FEM. The evaluation was not limited to classical mechanical parameters; it also comprehensively examined parameters that directly affect clinical outcomes, such as load transfer, contact pressure, deformation capacity, and long-term structural stability.

The results of the analysis revealed that the CoCr-UHMWPE combination was the most advantageous structure in terms of mechanical stability. This

combination, with its low maximum Von Mises stress (22.1 MPa), large contact area (112 mm²) and limited deformation (0.71 mm), allowed the load to be distributed more homogeneously among the prosthetic components. This offers clinically significant advantages in terms of wear resistance and the potential for long-lasting use of the prosthesis (3,4).

The Ti-UHMWPE combination showed the highest deformation trend (0.93 mm) due to its high modulus of elasticity. This deformation profile, together with the osteointegration capacity and low specific gravity of the Ti alloy, makes it a highly biomechanically compatible alternative for young and active individuals. However, it should be taken into consideration that risks such as creep formation and microscopic wear on the UHMWPE layer may occur in long-term use (2,7).

Although the CoCr-Ti combination limits the level of deformation due to high structural rigidity, the maximum Von Mises stress reaching 27.5 MPa and the narrow contact area (94 mm²) created high superficial stress accumulation, which increased the risk of local microcrack formation and implant loosening (11).

Overall, the CoCr-UHMWPE combination stands out as the most stable and reliable structural profile in terms of load-bearing balance, deformation control and contact stability in knee replacement applications. Although the Ti-UHMWPE combination stands out with its flexibility and biocompatibility advantages, it should be evaluated more carefully in terms of long-term structural stability. The CoCr-Ti combination, on the other hand, supports mechanical durability with its high stiffness, but carries the risk of microscopic damage due to local stress concentration.

In conclusion, the choice of material for knee replacement should not be limited to mechanical capability alone, but should be evaluated holistically with factors such as patient-specific clinical needs, activity levels and biological interactions. In the future, patient-specific FEM modeling, integration of functional gradient materials and personalized implant designs compatible with 3D manufacturing technologies will play a decisive role in increasing prosthesis longevity and surgical success rates.

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Ethical approval: Investigation of Material Effects in Knee Prosthesis Design Using Finite Element Method (FEM) since Finite Element Method is used in this publication, ethical approval is not required.

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What are the Anti-Rheumatic Drug Prescribing Patterns in Rheumatoid Arthritis Patients With Chronic Kidney Disease?: A Single-Center Cross-Sectional Study

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Abstract

Aim: This study evaluated the distribution of anti-rheumatic drug treatments in rheumatoid arthritis (RA) patients with chronic kidney disease (CKD) across different renal stages.

Material and Method: A cross-sectional analysis included 72 RA patients with CKD (estimated glomerular filtration rate <60 mL/min/1.73 m² for >3 months). Demographic characteristics, disease duration, laboratory results, current RA medications, and renal replacement therapy status were recorded. Additionally, the presence of extra-articular manifestations, comorbidities (including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, cerebrovascular disease, osteoporosis, and malignancy were obtained from the electronic patient files), history of prior infections, underlying etiology of CKD, and availability of renal biopsy reports were retrospectively extracted from hospital electronic medical records. Patients were stratified by CKD renal stage (3, 4, 5).

Results: Mean age was 66.7±11.8 years; 73.6% were female. Hypertension (84.7%) and diabetes (33.3%) were prevalent comorbidities. CKD etiology was undetermined in 65% of patients. Overall, 97.2% received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), 12.5% biologic disease-modifying antirheumatic drugs (bDMARDs), and 51.4% glucocorticoids. Hydroxychloroquine was the most common csDMARDs (76.4%), while methotrexate use differed significantly by CKD renal stage (stage 3: 27.7%; stage 4: 9.1%; stage 5: 0%; p=0.028). Among bDMARDs, rituximab (stage 3 only), TNF inhibitors (all stages), and tocilizumab (stage 4) were used. Etanercept was preferred in dialysis-dependent patients.

Conclusion: CKD stage significantly influences RA treatment selection. Methotrexate is avoided in stage 5 CKD, while hydroxychloroquine remains the predominant csDMARD. Leflunomide and sulfasalazine use in advanced CKD exceeds prior reports. Individualized therapy, adjusted for renal function and comorbidities, is essential. Larger prospective studies are needed to validate these findings.

Keywords: Antirheumatic agents, chronic renal insufficiency, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease characterized by articular and extra-articular involvement. RA is one of the most common systemic inflammatory diseases, affecting 0.6–1.0% of the general population (1). Its prevalence in Türkiye is 0.56% (2). The most prevalent comorbidity in RA patients is cardiovascular disease (3). Although determining the precise prevalence of chronic kidney disease (CKD) in RA patients can be challenging, CKD represents a substantial

proportion, affecting approximately 10-30% of patients (4-6). Nephropathy in RA can stem from drug toxicity (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, cyclosporin), secondary renal amyloidosis, or various glomerulonephritis (GN). Numerous studies have identified RA as a risk factor for reduced estimated glomerular filtration rate (eGFR) (5,7).

RA and CKD are chronic conditions that can mutually influence each other. While drugs used to treat RA can adversely affect the kidneys, the presence of CKD can

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complicate RA management. Since the metabolism and excretion processes of some medications used in RA treatment are renal, dose adjustments or alternative therapies may be necessary in this patient group. Therefore, regular patient monitoring and personalized treatment plans are critical. Controlling disease activity may prevent chronic inflammation from leading to kidney damage. Some studies suggest that treatments reduce the risk of CKD development (8).

Recent academic studies evaluating rheumatologic medications used in RA patients with CKD have particularly focused on the safety and efficacy of biological therapies (9-11). In this study, we aimed to evaluate not only biological therapies but all anti-rheumatic drug treatment preferences and their distribution according to renal stages.

MATERIAL AND METHOD

This cross-sectional study included 72 consecutive RA patients with CKD admitted to the Rheumatology Outpatient Clinic of Ankara Bilkent City Hospital between November 2022 and November 2023. All patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA (12). Exclusion criteria were defined as concurrent inflammatory rheumatic diseases, pregnancy, lactation and advanced liver failure that could affect our drug prescribing. Demographic characteristics, disease duration, laboratory results, current RA medications, and renal replacement therapy status were recorded. Additionally, the presence of extra-articular manifestations, comorbidities (including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, cerebrovascular disease, osteoporosis, and malignancy were obtained from the electronic patient files), history of prior infections, underlying etiology of CKD, and availability of renal biopsy reports were retrospectively extracted from hospital electronic medical records.

Recorded laboratory values included: Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, serum creatinine, eGFR, urine protein-to-creatinine ratio (UPCR).

Kidney function was evaluated using the eGFR (with the CKD-EPI formula). Patients with persistently reduced eGFR (<60 mL/min/1.73 m²) for >3 months were classified as having CKD, staged according to KDIGO guidelines as follows (13):

- **Stage 3:** eGFR 30–59 mL/min/1.73m² (moderate reduction)
- **Stage 4:** eGFR 15–29 mL/min/1.73m² (severe reduction)
- **Stage 5:** eGFR <15 mL/min/1.73m² (kidney failure)

Patients infection history was evaluated. Infections requiring hospitalization were classified as major infections, while those managed in outpatient settings were recorded as minor infections.

The data were analysed using the SPSS (version 22.0, IBM Corp., Armonk, NY, USA). The conformity of the numerical data to normal distribution was assessed

by both visual (Histogram and Detrended Q-Q charts) and analytical (Shapiro-Wilk or Kolmogorov-Smirnov tests) methods. Normally distributed numerical data were presented as mean±standard deviation, while non-normally distributed numerical data were presented as median (interquartile range). Categorical variables were presented as number (percentage). Chi-square tests were used to compare nonparametric data. p<0.05 was considered statistically significant.

The study was approved by the Ankara Bilkent City Hospital ethics committee (Approval no: E1-22-2932, Date: October 5, 2022) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

This study included 72 RA patients with CKD. The mean age was 66.74±11.80 years, and 73.6% (n=53) were female. The median disease duration was 13 years. RF and/or anti-CCP antibody positivity was present in 66.7% (n=48) of patients. Extra-articular involvement was observed in 11 patients (15.3%), comprising pulmonary involvement in 8 patients and cutaneous rheumatoid nodules in 3 patients.

The most prevalent comorbidities were hypertension (84.7%), diabetes mellitus (33.3%), hyperlipidemia (30.6%), coronary artery disease (30.6%), and osteoporosis (29.2%). Malignancy was present in one patient, who had dual malignancies (cervical and pancreatic cancer). A history of infection was reported in 36.1% of patients, the majority of which did not require hospitalization (Table 1).

Table 1. Characteristics of RA patients with chronic kidney disease	
Characteristic	
Age, years, mean (±SD)	66.74±11.80
Gender, Female, n (%)	53 (73.6)
BMI, kg/m ² , mean (±SD)	27.57±5.73
Disease duration (years), median (IQR)	13 (17)
Presence of autoantibodies, n (%)	
RF+ and Anti CCP+	32 (44.4)
RF or Anti CCP +	16 (22.3)
RF- and Anti CCP-	24 (33.3)
Extra-articular involvement, n (%)	11 (15.3)
Comorbidities, n (%)	
Hypertension	61 (84.7)
Diabetes mellitus	24 (33.3)
Hyperlipidemia	22 (30.6)
Coronary artery disease	22 (30.6)
Cerebrovascular disease	2 (2.8)
Osteoporosis	21 (29.2)
Malignancy	1 (1.4)
History of infection, n (%)	
Major	6 (8.3)
Minor	20 (27.8)
RA: rheumatoid arthritis, SD: standard deviation, BMI: body mass index, IQR: interquartile range, RF: rheumatoid factor, Anti CCP: anti-cyclic citrullinated peptide	

Laboratory parameters related to CKD are presented in Table 2. Regarding CKD etiology, the underlying renal cause was undetermined in the majority of patients. Among the known etiologies, diabetes and/or hypertension constituted the largest proportion. Other identified causes included nephrectomy due to calculi, hydatid cyst, NSAIDs associated nephritis, IgA nephropathy, post-infectious GN, membranous GN, minimal change disease, polycystic kidney disease, congenital solitary kidney, and renal amyloidosis secondary to long-term uncontrolled RA activity.

Concerning treatment, 97.2% of patients were receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), 12.5% biologic disease-modifying antirheumatic drugs (bDMARDs), and 51.4% glucocorticoids. Hydroxychloroquine was the most frequently used csDMARD, while methotrexate was the least used. Among bDMARDs, the most commonly used agents, in descending order of frequency, were rituximab, tumor necrosis factor inhibitors (TNFi), and tocilizumab. TNFi agents administered were etanercept (2 patients) and adalimumab (1 patient) (Table 2).

Table 2. Chronic kidney disease characteristics and medication preferences	
eGFR (ml/min/1.73m ²)	41 (29)
Serum creatinine (mg/dL)	1.47 (1.5)
UPCR (mg/g kreatinin)	395 (831)
Renal replacement therapy, n (%)	16 (22.2)
CKD etiology, n (%)	
Unknow	47 (65.3)
Diabetic and/or hypertensive	15 (20.8)
Nephrectomy	2 (2.8)
Amyloidosis	1 (1.4)
Others	7 (9.7)
Renal biopsy, n (%)	13 (18.1)
csDMARDs, n (%)	70 (97.2)
Methotrexate	14 (19.4)
Leflunomide	35 (48.6)
Sulfasalazine	20 (27.8)
Hydroxychloroquine	44 (61.1)
bDMARDs, n (%)	9 (12.5)
TNFi	3 (4.2)
Tocilizumab	2 (2.8)
Rituximab	4 (5.5)
GCs, n (%)	37 (51.4)

The results are presented in the form of median (Interquartile Range), or n (%); eGFR: estimated glomerular filtration rate, UPCR: urine protein-to-creatinine ratio, CKD: chronic kidney disease, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, bDMARDs: biological disease-modifying antirheumatic drugs, TNFi: tumor necrosis factor inhibitor, GCs: glucocorticoids

When patients were stratified into 3 groups based on CKD stage (stage 3, 4, 5), no significant differences were observed in the overall use of csDMARDs, bDMARDs, or

glucocorticoids between groups. However, a significant difference was found in methotrexate use (stage 3: 27.7%; stage 4: 9.1%; stage 5: 0%; p=0.028). Stage 3 patients most frequently received hydroxychloroquine and glucocorticoids, stage 4 patients received hydroxychloroquine and leflunomide, and stage 5 patients received hydroxychloroquine and leflunomide. methotrexate was not administered to any stage 5 patients. bDMARDs were used in 27.3% (3/11) of Stage 4 patients, compared to 10.6% (5/47) in Stage 3 and 7.1% (1/14) in Stage 5. TNFi use was equally distributed across all three CKD stages. All patients receiving tocilizumab therapy had stage 4 CKD, whereas all patients treated with rituximab had stage 3 CKD. One patient on tocilizumab had RA-associated secondary amyloidosis. Etanercept was the preferred bDMARD for one dialysis-dependent patient (Table 3).

Table 3. Drug preferences according to renal stages in CKD				
Drugs	Stage 3 n=47	Stage 4 n=11	Stage 5 n=14	p value
csDMARDs	47 (100)	10 (90.9)	13 (92.9)	0.122*
Methotrexate, n (%)	13 (27.7)	1 (9.1)	0 (0)	0.028*
Leflunomide, n (%)	22 (46.8)	6 (54.5)	7 (50.0)	0.943*
Sulfasalazine, n (%)	12 (25.5)	4 (36.4)	4 (28.6)	0.798*
Hydroxychloroquine, n (%)	29 (61.7)	7 (63.6)	8 (57.1)	0.936*
GCs, n (%)	28 (59.6)	4 (36.4)	5(35.7)	0.165*
bDMARDs, n (%)	5 (10.6)	3 (27.3)	1 (7.1)	0.296*
TNFi	1 (2.1)	1 (9.1)	1 (7.1)	
Tocilizumab	0 (0)	2 (18.2)	0 (0)	
Rituximab	4 (8.5)	0 (0)	0 (0)	

Due to small sample sizes in Stage 4 and Stage 5, particularly for bDMARD subgroups, statistical comparisons (p-values) for these groups should be interpreted with caution; * Chi-square tests; CKD: chronic kidney disease, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, GCs: glucocorticoids, bDMARDs: biological disease-modifying antirheumatic drugs, TNFi: tumor necrosis factor inhibitor

DISCUSSION

This study analyzes demographic characteristics, comorbidities, renal etiology, and treatment approaches in RA patients with concomitant CKD. Our findings highlight critical clinical patterns in this specific population, including a high comorbidity burden, uncertainty regarding renal etiology, and CKD stage-specific the real-world prescribing patterns of anti-rheumatic medications in RA patients. Unlike some previous studies primarily focused on bDMARDs, this research provides a valuable assessment of the utilization of all major anti-rheumatic drug classes – csDMARDs, bDMARDs, and glucocorticoids – within this specific patient group.

We observed a csDMARD utilization rate of 97.2% and a bDMARDs utilization rate of 12.5% among our RA patients with CKD. Hydroxychloroquine was the most frequently used csDMARD, while methotrexate was the least used. Our methotrexate usage was approximately 20%, and notably, it was not administered to any stage 5 CKD patients. A

previous study evaluating RA patients with CKD receiving biologic therapy reported methotrexate usage near 50%, although it did not provide a separate assessment by renal stage (14). In our study, the classification of patients according to established CKD stages (3, 4 and 5) is a major strength. This detailed analysis provides important clinical stage-specific information by demonstrating how treatment options, particularly for nephrotoxic or renally cleared drugs such as methotrexate, significantly change with decreasing renal function. Similarly, a study evaluating RA patients with end-stage renal disease (ESRD) also reported no methotrexate use, consistent with our findings in stage 5 patients. In that study, half the patients used glucocorticoids and hydroxychloroquine was the most frequently used csDMARD, while other csDMARDs were rarely used (15). In contrast, within our stage 5 patient group, hydroxychloroquine (57.1%) was also the most common, but leflunomide (50%) and sulfasalazine (28.6%) usage was more prevalent than reported in the aforementioned study. The findings regarding the relatively frequent use of leflunomide and sulfasalazine in Stage 4 and Stage 5 CKD patients, exceeding rates previously reported in the literature, constitute an important contribution. This suggests evolving clinical practices or better recognition of their adjusted dosing feasibility in severe renal impairment. Current ESRD treatment recommendations advise that leflunomide dosing requires no adjustment, sulfasalazine requires a 50% dose reduction, and methotrexate is contraindicated (16). Our findings align with these recommendations.

The most frequently used bDMARDs in our study were rituximab, TNFi agents and tocilizumab, respectively. In contrast to our results, previous studies demonstrated that TNFi were the most frequently preferred bDMARDs, with etanercept being the most commonly selected agent within the TNFi class (14,15). In our study, etanercept was the only TNFi agent administered to patients receiving renal replacement therapy. TNFi agents remain central to RA treatment due to their well-documented efficacy and safety profile. As they are primarily metabolized in lysosomes, their pharmacokinetics are not significantly influenced by renal function (17). The preference for etanercept in our ESRD group may be attributed to its shorter half-life, potentially offering a safety advantage in the context of impaired kidney function (14). Rituximab is known to be usable in CKD patients without requiring dose adjustment (16). All four patients receiving rituximab in our study had stage 3 CKD, and one had a concomitant malignancy diagnosis. A previous Turkish study in RA patients with CKD reported rituximab usage rates similar to ours (18).

When examining bDMARDs use by CKD stage, it was most prevalent in stage 4 CKD patients, among whom tocilizumab usage was common. One patient receiving tocilizumab had a diagnosis of RA-associated secondary amyloidosis. Secondary amyloid A (AA) amyloidosis is a rare and potentially fatal complication observed in patients with long-standing, refractory RA (19). Suppression of serum amyloid A (SAA) protein production is essential for

controlling AA amyloidosis. SAA is synthesized in the liver in response to stimulation by pro-inflammatory cytokines such as interleukin-6 (IL-6), TNF, and interleukin-1. Consequently, reducing the levels of these cytokines is crucial for lowering SAA. While TNF inhibition can decrease SAA levels, normalization of SAA levels has been specifically achieved through IL-6 blockade (20,21). These literature findings support our rationale for prioritizing tocilizumab in patients with amyloidosis.

As the population of RA patients ages, an increase in comorbidities, including CKD, is anticipated. However, the precise frequency of CKD in RA patients and the extent to which common RA comorbidities like hypertension and diabetes contribute to ESRD development remain unclear (15). The most prevalent comorbidities in our cohort—hypertension, diabetes mellitus, hyperlipidemia, and coronary artery disease—are consistent with previous literature (14,18). A prior study conducted at our clinic evaluating comorbidities in inflammatory rheumatic diseases reported a CKD prevalence of 2% in RA patients (22). Other studies, however, have reported higher prevalence rates, ranging from 10% to 30% [4-6]. Conversely, a study examining RA prevalence among ESRD patients found it to be approximately 1% (15).

Extra-articular involvement occurs in approximately 40% of RA patients (23). The subclinical nature of pulmonary disease in many RA patients makes precise epidemiological assessment challenging. A study employing computed tomography (CT) screening in RA patients reported pulmonary involvement in 8% of cases, with interstitial lung disease (ILD) in 52%, pulmonary rheumatoid nodules in 5%, pleural effusion in 3%, and drug-induced lung disease in 3% of those affected (24). Our study did not include systematic CT screening; pulmonary involvement was recorded retrospectively, and ILD was noted in approximately 11% of patients. This finding suggests that pulmonary involvement might be more frequent in RA patients with CKD. This could be explained by several factors in our CKD cohort: older age, longer disease duration, and the potential for uremia and toxin accumulation to exacerbate inflammatory responses, leading to lung tissue damage. Furthermore, medications like methotrexate, used in RA treatment, may contribute to pulmonary fibrosis via drug toxicity in CKD patients.

Regarding CKD etiology, the cause remained unknown in 65% of our patients. This likely stems from the retrospective nature of data extraction from hospital electronic records and potential limitations within the record-keeping system. Among identified causes, diabetes and hypertension were the most common. A study evaluating RA patients with ESRD also identified diabetes and hypertension as the primary etiologies. Miscellaneous causes constituted about 8% in that study, significantly lower than in ours; this discrepancy may be explained by more comprehensive retrospective data in their cohort (15). RA-associated amyloidosis accounted for approximately 1% of cases in our study. While amyloidosis was historically suggested

as one of the most common causes of renal involvement in RA (25,26), more recent studies support our findings, indicating a diminished prevalence of amyloidosis in RA (15,27). CKD associated with NSAIDs was observed in approximately 1% of our patients, which is consistent with the findings from the ESRD study (15).

Our study has several limitations. It is a cross-sectional analysis conducted on a relatively small patient population. This constrains our statistical power and may have impacted the feasibility of robust subgroup analyses. Consequently, caution is warranted when generalizing our findings to the broader CKD population. Certain patient information was collected retrospectively by reviewing medical records. This approach introduces risks of missing data, potential effects of recording errors, and the inherent potential for bias associated with retrospective data collection. Our study lacks a control group comprising RA patients without CKD. This omission limits our ability to make direct comparisons regarding the impact of CKD on RA treatment choices. The study protocol did not systematically capture data on dose reductions or treatment regimen modifications specifically made due to CKD. This gap precluded our ability to assess the practical implications of renal dysfunction on RA treatment management and its potential association with treatment response. The presence of malignancy is an important parameter affecting treatment decisions. The inclusion of these patients is another limitation of the study, but only one patient in our study had malignancy. Future research should involve larger, prospective, controlled, multicenter cohort studies to enhance the generalizability of findings. If feasible, longitudinal follow-up would be valuable to investigate the relationship between CKD progression and RA activity/treatment response.

CONCLUSION

This study demonstrates significant clinical patterns in RA patients with CKD. Treatment approaches were influenced by CKD stage, highlighting its impact on pharmacological selection. While csDMARDs were widely utilized, methotrexate use was notably low and entirely contraindicated in stage 5 CKD patients due to safety concerns. Hydroxychloroquine emerged as the most frequently prescribed csDMARD. Conversely, the use of leflunomide and sulfasalazine in stage 5 CKD patients exceeded rates previously reported in the literature. The management of RA in the context of CKD represents a complex clinical challenge, necessitating individualized treatment strategies attuned to renal function stage and aggressive management of comorbidities. Our findings underscore the need for larger, multicenter, prospective controlled studies to further validate these observations and enhance their generalizability.

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Investigation of Inferior Vena Cava Diameter Measurements as An Assessment Criterion in Acute Dehydration

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Abstract

Aim: Acute dehydration due to gastroenteritis is a significant and preventable cause of childhood mortality worldwide. "We used bedside ultrasonography to compare inferior vena cava/Abdominal aorta (IVC/Ao) diameter ratios before and after treatment in patients with acute dehydration and controls, offering a novel, rapid, and objective assessment tool.

Material and Method: This study included 68 children admitted to Düzce University Medical Faculty Hospital Pediatric Emergency. 34 of them were patients had acute severe dehydration, and the other 34 case were in the healthy Control Group (CG). IVC and Ao were measured in the transverse plane below the xiphoid process using bedside ultrasonography (USG).

Results: A significant difference was found in the IVC/Ao ratio between the Patient Group (PG) and CG ($p < 0.001$). When PG pre- and post-treatment measurements were compared, the results were highly significant ($p < 0.001$). The lack of correlation between the IVC/Ao ratio and age and weight demonstrated that it could be used in the assessment of children of all ages and weights.

Conclusion: The IVC/Ao ratio is a rapid and innovative assessment method that can be applied across various age groups and weight categories.

Keywords: Acute gastroenteritis, acute dehydration, bedside ultrasonography, inferior vena cava, abdominal aorta diameter

INTRODUCTION

Dehydration due to acute gastroenteritis is the second most common cause of childhood mortality with a rate of 9%. Worldwide, 710.000 children die each year due to acute dehydration throughout the World (1,2). Acute gastroenteritis in children cause 1.5 million outpatients, 200,000 hospitalizations, and 300 deaths annually in the United States (3). The fact that acute dehydration can be easily treated with appropriate fluid replacement makes this situation more dramatic.

The global mortality rate has started to decline rapidly in the last decade, with the incidence of diarrhea decreasing from 3.4 per hundred thousand to 2.9 per hundred thousand per year. Diarrhea mortality rates have decreased, although

minor changes have occurred, such as rotavirus vaccine, improvements in infant nutrition, Oral Rehydration Fluid, and changes in the diet of children with diarrhea (4). New treatment and diagnostic methods for pediatric diarrhea will play an important role in reducing mortality (5).

In cases of no dehydration or mild dehydration, there is no need for examination. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2014 guidelines do not recommend the routine use of any stool test to differentiate bacterial viral diarrhea (6-8). Thus, the lack of a definite laboratory value for acute dehydration causes the diagnosis, follow-up, and treatment of the patient to be non-specific, which causes uncertainty in the duration, amount, and adequacy of treatment.

CITATION

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The most important goal in the treatment of dehydration due to acute gastroenteritis is to maintain the fluid and electrolyte balance and restore hydration. Breastfed infants should continue to be breastfed (5,6).

Adequate and safe treatment of a condition with such a high incidence in children will be possible with the use of measurements that determine the diagnosis and degree of dehydration, and mortality will decrease significantly. This will provide numerical information regarding the adequacy of treatment.

MATERIAL AND METHOD

34 patients between the age range of 6 months-11 years, admitted to Düzce University Medical Faculty Hospital within six months, and who developed acute dehydration due to acute gastroenteritis were included in the Patient Group. 34 healthy patients without acute dehydration or acute gastroenteritis were included in the study as the Control Group. Our study was approved by Düzce University Medical Faculty Hospital Ethics Committee on 27.06.2016 with the number 2016/53, and conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Patients with acute gastroenteritis who visited the Pediatric Emergency department with complaints of vomiting and diarrhea were evaluated by the pediatrician in charge. No intervention was performed for the treatment and examinations were decided by the clinician. The patients considered to have acute dehydration due to acute gastroenteritis were reported to the researcher, who was questioned again according to the World Health Organization (WHO) dehydration rating in terms of dehydration and acute gastroenteritis (9). The control group comprised patients who presented to the pediatric emergency department with general symptoms and abdominal pain. These group consisted of healthy children without any current infection or history of acute or chronic illness. All participants underwent examination and diagnostic workup to confirm the absence of pathology and none required hospital admission.

The patient (PG) and control (CG) groups were evaluated according to the WHO Dehydration scale. This case form included clinical conditions based on the WHO scale (vomiting episodes, thirst, urine output, general appearance, eyes, skin turgor, mucosal membranes, tears, pulse quality, respiratory pattern, and capillary refill time). This study included patients observed in the pediatric emergency department who presented with severe dehydration, as determined by the World Health Organization dehydration scale, and who subsequently required intravenous fluid resuscitation. The examination findings and treatment were recorded on the case form by a pediatrician who conducted the examination according to the WHO dehydration scale. Data from case forms were retrospectively included in the study.

Ultrasonographic Measurement

Prior to the study, the researcher received training in bedside USG. Abdominal Aorta (Ao) and inferior

vena cava (IVC) measurements were performed with ultrasonography (USG) in the Pediatric Emergency department (General Electric/LOGIQ A5 Pro Model). The measurements were performed anteroposterior (AP) from below the xiphoid with the convex probe at 5.0 MHz frequency, in the transverse section images of the pediatric abdominal preset. The diameters of the Ao and IVC were measured by the researcher in a single view section. To increase the statistical accuracy and reduce the clinical error in the measurements made in 68 cases, two separate measurements of Ao and IVC were performed consecutively, and their average was calculated.

Measurements were recorded before and within 2-4 hours of treatment in the Patient Group at two separate times. This was recorded once for the Healthy Control Group. The workflow and overall applications are presented in Figure 1.

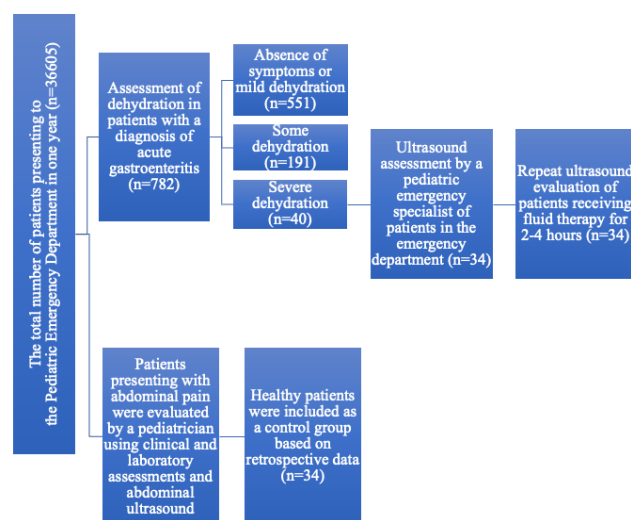


Figure 1. Emergency department evaluation process for pediatric dehydration in gastroenteritis

Exclusion criteria of the study: Patients presenting with vomiting except for severe sepsis and acute gastroenteritis, chronic gastroenteritis (>2 weeks), intoxication, congenital heart disease, heart failure, acute trauma, acute blood loss, and connective tissue diseases such as Marfan syndrome, with other chronic diseases, who received oral free liquid as treatment and 20 ml/kg saline within less than two hours were excluded from the study.

Statistical Analysis

The analysis was conducted using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive data are expressed as mean±standard deviation for continuous variables and as frequency and percentage for categorical variables. Depending on the distribution of the data, the Independent Samples t-test or Mann-Whitney U test was used to compare the groups in terms of continuous variables. The relationships between categorical variables were examined using the chi-square test or Fisher's exact test, depending on the expected value rule. In the comparison of the Patient Group before and after treatment, the Paired Samples t-test or Wilcoxon test was used depending on the distribution of the data for continuous variables, and McNemar or McNemar-Bowker tests were

used for categorical variables, depending on the number of categories. Pearson’s correlation analysis was used to examine the linear relationship between the continuous variables. Statistical analyses were performed using SPSS software, and the significance level was set at 0.05.

RESULTS

Demographic Characteristics and Laboratory

The mean age of the participants in the PG was 52.85±34.34 months (min 8 months; max 132 months). In the CG, the mean age was 44.35±31.29 months (min 6 months; max 120 months). The mean weight of PG was 16.75±7.14 kg and the mean weight CG was 17.88±8.73 kg. Fifteen (44.1%) participants in the PG and 14 (41.2%) in the CG were females.

There were no significant differences between the two groups in terms of age, sex, or weight (age, p=0.29; sex, p=0.56; weight, p=0.8).

Compared to controls, patients showed significant differences in the following laboratory values: White blood cell (PG;10.78±4.88 and CG;8.81±2.50, p=0.042), Sodium (PG;137.35±4.21 and CG;145.26±2.16, p=0.001), K (PG; 4.42±0.49 and CG; 4.74±0.34, p=0.003), Urea (PG; 30.10±12.93 and CG; 20.96±6.39, p=0.001), BUN (PG;14.11±5.86 and 9.99±3.04, p=0.001), Creatinine (PG; 0.44±0.16 and CG;0.34±0.11, p=0.003), and C-reactive protein (PG;16.2±10.4 and 3.5±3.1, p=0.001). There were no significant differences in Hb, Htc, and Cl between the groups (Table 1).

Table 1. Patient group and control group laboratory values			
	Patient group (n=34)	Control group (n=34)	p value
Hb	12.14±1.16	11.83±0.85	0.223
Htc	36.75±3.39	35.74±2.38	0.162
Wbc	10.78±4.88	8.81±2.50	0.042
Na	137.35±4.21	145.26±2.16	0.001
K	4.42±0.49	4.74±0.34	0.003
Cl	102.71±5.64	102.62±2.12	0.932
Urea	30.10±12.93	20.96±6.39	0.001
BUN	14.11±5.86	9.99±3.04	0.001
Creatinin	0.44±0.16	0.34±0.11	0.003
CRP	16.2±10.4	3.5±3.1	0.001

Hb: hemoglobin, Htc: hematocrit, Wbc: white blood cells, Na: sodium, K: potassium, Cl: chloride, BUN: blood urea nitrogen, CRP: C-reactive protein

The causative agents of gastroenteritis identified in our study were as follows: Rotavirus (n=24), Adenovirus (n=5), and Unknown (n=5).

Examination Findings

In PG, 20 individuals (58.8%) experienced reduced or no urine output. Mucosal hydration assessment revealed 4 cases (11.8%) with dry mucosa, 21 cases (61.8%) with moderately dry mucosa, and 9 cases (26.5%) with slightly dry or moist mucosa. Significant differences were observed between PG and CG in terms of urine output, thirst sensation, mucosal hydration (p<0.001), and tear production (p=0.011).

However, no statistically significant differences were found between the groups in terms of turgor tone, capillary refill time, pulse quality, respiratory evaluation, and extremity temperature.

Comparisons within the patient group before and after treatment revealed significant improvements in the thirst sensation (p=0.039), mucosal hydration (p<0.001), and tear production (p=0.031). The average peak heart rate decreased from 100/min before treatment to 90/min after treatment (p=0.005). These findings suggest that fluid therapy results in reduced thirst, improved mucosal hydration, increased tear production, and decreased tachycardia. These results emphasize the importance of assessing urine output and thirst in acute dehydration, along with the evaluation of mucosal hydration.

Ultrasonography Findings

Before the PG treatment, the mean IVC was 0.50±0.16 mm, and the mean Ao was 0.83±0.17 mm. The mean IVC/Ao ratio were 0.61±0.18. The mean IVC in CG was 0.85±0.18 mm, and the mean of Ao was 0.86±0.17 mm. IVC/Ao ratio was found to be 0.99±0.09. The IVC/Ao ratio between CG and PG found a difference (p<0.001) (Table 2).

The In PG-PreTreatment and PG-postTreatment measurements, IVC PG-PreTreatment mean was 0.50±0.16 mm, and the mean of IVC PG-PostTreatment was 0.72±0.21 mm (p<0.001). The mean Ao PG-PreTreatment was 83±0.17 mm and the mean Ao PG-PostTreatment was 83±0.18 mm. This result demonstrates that the Ao Diameter before and after dehydration can be a constant measurement that does not change. IVC/Ao ratio in PG-PreTreatment was 0.61±0.18, and 0.87±0.17, respectively (p<0.001). One of the positive results of the study was that the IVC/Ao ratio increased in favor of IVC and approached Ao after treatment (Table 2).

Table 2. IVC diameter, Ao diameter and IVC/Ao ratio; p value between PG-CG and patient group pre-treatment and post-treatment					
	Patient group Pre-treatment (n=34)	Control group (n=34)	p value Between PG-CG	Patient group Post-treatment (n=34)	p value between pre-post treatment
IVC	0.50±0.16	0.85±0.18	<0.001	0.72±0.21	<0.001
Ao	0.83±0.17	0.86±0.17	0.492	0.83±0.18	0.979
IVC/Ao	0.61±0.18	0.99±0.09	<0.001	0.87±0.17	<0.001

IVC: inferior vena cava, Ao: abdominal aorta, PG: patient group, CG: control group

The correlations of IVC, Ao, and IVC/Ao with age and body weight of the PG and CG were evaluated. Highly significant results were obtained in the Pearson correlation with IVC age (months) and body weight in the CG ($r=0.659$, $p<0.001$). Pearson correlation was found to be significant for Ao ($r=0.713$, $p<0.001$). Indeed, this result was expected. Age and weight were not significant in all correlations, including the IVC/Ao ratio, CG, PG-PreTreatment, and PG-PostTreatment. This shows that the IVC/Ao ratio was not affected by variables, such as age and weight (Table 3).

Table 3. The correlations of IVC diameter, Ao diameter and IVC/Ao with the ages and body weights			
		Age (month)	Body weight (kg)
IVC pre-treatment	r	0.628*	0.515*
	p	<0.001*	0.002*
	n	34	34
IVC post-treatment	r	0.741*	0.462
	p	<0.001*	0.006*
	n	34	34
Ao pre-treatment	r	0.678*	0.618*
	p	<0.001*	<0.001*
	n	34	34
Ao post-treatment	r	0.742*	0.461
	p	<0.001*	0.006*
	n	34	34
IVC/Ao pre-treatment	r	0.149	0.086
	p	0.399	0.629
	n	34	34
IVC/Ao post-treatment	r	0.299	0.216
	p	0.086	0.219
	n	34	34

IVC: inferior vena cava, Ao: abdominal aorta diameter

DISCUSSION

Although clinical anamnesis and physical examination are at the center of the diagnosis and treatment of acute dehydration in pediatric patients, this evaluation can be reflected in the treatment and follow-up in different ways, depending on the patient's anamnesis and the clinician's approach. However, laboratory evaluations do not provide clear data for clinicians. In this respect, approaching a clear measurable value in patients undergoing acute dehydration will be useful in terms of treatment and follow-up. It is very important that there is a measurement in the denominator of the ratio to be evaluated that is not affected by age, weight, or acute dehydration. Therefore, it appears that Ao is not affected by intravenous or oral treatments (10,11). In addition, Ao is directly correlated with age and weight. In this case, Ao allowed us to obtain a value independent of age and weight when proportioned to the IVC at different ages and weights. IVC diameter and IVC/Ao ratio were significant before and after treatment.

According to the data in the study, white blood cell count, sodium, potassium, urea, BUN, creatinine, and CRP levels are significantly different in dehydrated children compared to the control group (Table 1). Notably, changes in sodium and potassium levels highlight that electrolyte imbalances are a significant consequence of dehydration (12). The observed changes in Na levels in our study corroborate these findings, further indicating the impact of dehydration. Increased urea, BUN, and creatinine levels compared to the control group suggest an effect on kidney functions, although these values remained within normal limits. The increase in CRP value indicates that the body is undergoing an inflammatory response. This collectively illustrates how dehydration affects the physiological balance in children and triggers the inflammatory response. The pathophysiology of dehydration involves a loss of bodily fluids, which can lead to electrolyte imbalances, alterations in renal function, and the activation of inflammatory processes. Early diagnosis and intervention are crucial to prevent serious complications such as acute kidney injury (13).

In Modi et al.'s research, a statistically significant relationship was discovered between the diameters of the aorta and IVC. However, the study also cautioned that the substantial increase in IVC diameter following fluid therapy in severely dehydrated children cannot be relied upon as a dependable measure (14). It is our belief that the IVC, which is subject to various influences, should not be considered in isolation, and that a more accurate result can be obtained by utilizing the IVC/Ao ratio. The disparity in the IVC/Ao ratio between the healthy control group and post-treatment group in our study implies that dehydration-induced intravascular volume loss can be replenished with long-term oral fluid therapy. Our study allowed for unrestricted access to oral rehydration therapy. Based on this observation, we infer that assessment of severely dehydrated patients can be carried out using adequate fluid therapy, and the results can be assessed through subsequent evaluations.

One of the challenges associated with measuring IVC is that it is influenced by various factors. The standardization of measurements can be affected by the collapse of inspiratory and respiratory cycles. Although weight is not directly related to this situation, it can lead to difficulties for clinicians in determining the accuracy of measurements (15-17). To address this issue, our study obtained the largest portion of IVC measurement close to the expiration time and calculated the average of two separate measurements. We believe that this approach can improve standardization. In the study by Jauregui et al., an IVC/Ao ratio of 0.83 or higher was considered normal (16). In a study by Kwon et al., the IVC/Ao ratio was 0.54 in dehydrated patients (18). Naghipour et al. suggested that the IVC/Ao ratio was the most reliable indicator for transesophageal echocardiography in healthy children, and the mean ratio measured at the right atrium entrance was reported as 0.94 (19). In our study, the IVC/Ao ratio was 0.61 before treatment and increased to 0.87 after treatment, and it was 0.99 in the Control Group (Table 2). The values obtained in our study are consistent with those

reported in other studies, indicating that the IVC/Ao ratio can be safely used in most patient

In a study conducted by Özkan et al., 128 children with dehydration were classified into three groups based on dehydration severity: mild, moderate, and severe. Significant differences were observed in the IVC/Ao ratio between the pre- and post-treatment groups. Additionally, a meaningful difference in p value was found between the CG and PG groups in our study, which was conducted in addition to the comparison of pre- and post-treatment values (Table 2) (20).

In a prior investigation, Bellini et al., 65 patients were diagnosed with IVC collapse. This was assessed by using the Kiss-Sing score. This finding suggests a link between dehydration and the development of IVC. In addition, this study did not find a correlation between IVC measurements and biomarkers related to biochemical parameters. Our study included a control group and dehydration scale, which allowed for a more comprehensive evaluation of the IVC/Ao ratio (21).

In a comprehensive meta-analysis carried out in 2023, Kaminecki et al. scrutinized the findings of eight individual studies. The authors posited that the World dehydration assessment tool was the most effective measurement tool, and the results indicated the importance of maintaining proper hydration levels in pediatric patients (22). In our study, we observed a substantial increase in the post-dehydration IVC diameter in three of the studies included in the aforementioned meta-analysis. Additionally, our study demonstrated a noteworthy increase in the IVC/Ao ratio post-treatment, with a difference of pre-treatment.

Limitations: The fact that this was a single-center study, USG was performed by a single clinician, and children under the age of two are incompatible while performing USG, which limits the results of the study. The retrospective design of this study precluded the inclusion of urine output as a variable. Prospective studies should address this limitation by recording and analyzing the relationship between urine output, treatment duration, and IVC measurements in dehydrated patients to facilitate a more comprehensive comparison of IVC diameters. While not consisting entirely of healthy children, the control group for this study included patients presenting to the emergency department who did not meet the inclusion criteria for dehydration-related illnesses.

CONCLUSION

The IVC/Ao ratio is a fast and reliable numerical ratio that can be used in the diagnosis, treatment, follow-up, and clinical evaluation of patients with acute dehydration.

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Systemic Inflammatory Markers (NLR/PLR) and Climatic Factors as Predictors of Severity in Pediatric Carbon Monoxide Poisoning

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Abstract

Aim: Carbon monoxide (CO) poisoning remains a global health challenge, particularly in developing nations. This study evaluates the prognostic role of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and climatic parameters in pediatric CO poisoning severity.

Material and Method: In this retrospective cohort study, 132 pediatric patients admitted to a tertiary emergency department were stratified by carboxyhemoglobin (COHb) levels (mild: <5%; moderate: 5–25%; severe: >25%). Associations between NLR/PLR, meteorological data (temperature, wind speed, air pressure), and clinical outcomes were analyzed.

Results: Severe cases exhibited significantly elevated NLR (2.09 [IQR 1.24-3.54]; $p=0.019$) and PLR (106.2 [80.6-164.4]; $p=0.032$) compared to others, alongside higher COHb (31.45 [27.25-34.2]; $p<0.001$) and lactate (2.7 [1.8-3.45] mmol/L; $p=0.07$). Central nervous system symptoms (CNS) predominated in severe poisoning (28.6%, $p=0.014$). Maximum temperature was inversely correlated with severity ($p=0.032$).

Conclusion: NLR and PLR serve as early indicators of CO poisoning severity, while higher air temperatures reduce risk. These findings support using routine hemogram indices for risk stratification and underscore the need for climate-aware public health interventions.

Keywords: Carbon monoxide poisoning, air temperature, children, systemic immune/inflammatory index markers, temperature

INTRODUCTION

Carbon monoxide (CO), a colorless, odorless, and tasteless gas, is produced by the incomplete combustion of carbon-containing fuels. It is a significant air pollutant emitted from sources such as engine exhausts and fires. In many regions, especially in developing countries, CO poisoning often results from the inadequate burning of wood or coal used for heating during cold weather or for activities like cooking and baking (1). Once inhaled, CO binds to hemoglobin with an affinity approximately 250 times greater than oxygen, forming carboxyhemoglobin (COHb). This process reduces hemoglobin's oxygen-carrying capacity, leading to tissue hypoxia (2). Clinically, CO poisoning can present with nonspecific symptoms

such as headache, dizziness, and nausea, or progress to severe neurological manifestations, including loss of consciousness and death (3). Notably, symptom severity does not always correlate with COHb levels, making early diagnosis and intervention critical (4). Children are particularly vulnerable due to their higher metabolic rates, increased respiratory rates relative to body surface area, and limited ability to articulate symptoms (5). Delayed recognition of CO poisoning can result in long-term neurological sequelae, underscoring the need for effective diagnostic and prognostic tools.

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), derived from routine complete blood counts, are emerging as systemic immune/

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inflammatory markers. Initially studied in malignancies, these indices are increasingly used to assess inflammation and predict outcomes in pediatric diseases (6). Their accessibility and low cost make them promising candidates for evaluating CO poisoning severity (7).

CO poisoning exhibits seasonal patterns, with higher incidence during winter months when low temperatures, reduced wind speeds, and increased indoor heating contribute to gas accumulation in enclosed spaces (8). Despite global awareness, CO poisoning remains a persistent public health challenge, particularly in developing nations (9). Early prediction of poisoning severity is essential to mitigate adverse outcomes.

This study investigates the relationship between climate parameters (e.g., temperature, humidity, wind speed, air pressure), systemic inflammatory markers (NLR, PLR), and CO poisoning severity in pediatric patients. By analyzing these factors, we aim to identify accessible prognostic indicators and environmental risk factors to improve clinical management and prevention strategies.

MATERIAL AND METHOD

Study Design

This study is a retrospective cohort study conducted in the pediatric emergency department of Aksaray Training and Research Hospital, a tertiary level university hospital.

Study Population

The study included 235 pediatric patients aged 1 month to 18 years who were admitted to the Aksaray Training and Research Hospital Pediatric Emergency Department with CO poisoning between 2017 and 2024. A total of 103 patients whose climate parameters were not accessible before 2018 and after August 2023 were excluded from the study. A total of 132 patients were included in the study.

Data Collection

The data in the study were obtained retrospectively from the hospital data system. Demographic characteristics of the patients such as age, gender, and nationality, admission date, day, time, time zone, patient's arrival symptoms, COHb level at the time of admission date, hemoglobin (g/L), neutrophil (mm^3), lymphocyte (mm^3), platelet (mm^3), blood gas parameters, albumin (g/L), C-reactive protein (CRP) (mg/L), troponin (pg/mL), follow-up period, and control laboratory parameters were obtained retrospectively from the hospital information system and recorded. Climate parameters were obtained from the Meteorology Department of the Ministry of Environment, Urbanization and Climate of the Republic of Türkiye. Air temperature ($^{\circ}\text{C}$), humidity (g/m^3), wind speed (Knot), wind direction, and air pressure (mb) on the days when the patients applied were recorded.

In our study, patients were stratified by age (<5 years and ≥ 5 years) and categorized into three exposure subgroups:

stove-related, natural gas-related, and other sources (e.g., fires, vehicle exhaust, hookah). Clinical presentations were classified by system involvement: respiratory system (shortness of breath, cough, tachypnea), central nervous system (CNS) (seizures, confusion, dizziness, headache), or gastrointestinal system (GIS) (vomiting, nausea, abdominal pain).

Disease severity was defined by admission COHb levels: mild (COHb<5%), moderate (COHb: 5–25%), or severe (COHb>25%). This stratification enabled systematic analysis of demographic, clinical, and environmental correlations with poisoning severity (7).

Ethics

Aksaray University Health Sciences Scientific Research Ethics Committee approved the decision dated 05.12.2024 and numbered SAGETIK134.

Statistical Analysis

The normality of variable distributions was assessed through multiple approaches, including visual inspection of histograms and quantitative measures (kurtosis, skewness), supplemented by the Kolmogorov-Smirnov test. For non-normally distributed variables, we employed non-parametric tests: the Mann-Whitney U test for comparisons between two independent groups and the Kruskal-Wallis test for analyzing CO poisoning severity classifications. These non-parametric results are presented as medians with interquartile ranges (IQR-25-75). Categorical variables were evaluated using the Chi-square test, with post-hoc analyses (adjusted residuals with Bonferroni correction) to identify specific subgroup differences when significant overall effects were detected.

RESULTS

The study cohort comprised 132 pediatric patients, with a near-equal gender distribution (47% female [$n=62$]; 53% male [$n=70$]). The majority (92.4%) were Turkish nationals, while 7.6% were refugees. Patients had a mean age of 115.80 ± 65.202 months (approximately 9.7 years), with 28.8% ($n=38$) aged ≤ 5 years and 71.2% ($n=94$) > 5 years. When the application times of the patients were examined: 76% of admissions occurred during winter months, with February accounting for 40% of cases. Weekly distribution showed Wednesday as the most common admission day (peak frequency), while diurnal patterns demonstrated that 38.6% of presentations clustered between 08:00-16:00. Patients predominantly presented with respiratory (39.4%, $n=52$; cough/respiratory distress) or GIS (33.3%, $n=44$; nausea/vomiting) symptoms. Neurological symptoms occurred in 27.3% ($n=36$), ordered by decreasing frequency: confusion ($n=14$), headache ($n=12$), dizziness ($n=8$), and seizures ($n=2$), reflecting progressive CNS involvement. The average time between poisoning and hospital admission was 1.6 ± 0.516 hours. Demographic data are summarized in Table 1.

Initial laboratory evaluation revealed the following key findings (presented as mean±SD): Hematologic parameters included elevated white blood cells (WBC 10.45±3.89/mm³), platelets (318.45±77.99/mm³), and neutrophil predominance (5.96±3.32/mm³), with corresponding systemic inflammatory indices (NLR 2.55±2.77; PLR 117.01±71.50). We found that there was a metabolic disorder in biochemical markers: lactic acidosis (lactate 2.36±1.23 mmol/L; pH 7.35±0.58), elevated cardiac enzymes (CK 182.9±441.7 U/L; CK-MB 29.91±16.61 U/L; troponin 28.02±205.04 pg/mL), and mild hypoalbuminemia (44.42±3.84 g/L). Blood gas analysis showed significant hypoxia (PaO₂ 36.4±21.14 mmHg) with compensatory respiratory alkalosis (PCO₂ 40.85± 7.44 mmHg; HCO₃⁻ 22.41±2.81 mmol/L). The mean COHb level confirmed substantial exposure (15.84±9.37%), while CRP (2.70±12.31 mg/L) indicated modest systemic inflammation.

Analysis of meteorological conditions during patient admissions revealed the following patterns (mean±SD): maximum wind speed (10.03±5.34 knots), average wind speed (2.42±1.36 knots), barometric air pressure (904.48±6.87 mb), and air temperatures (average: 6.54±7.84°C; maximum: 11.21±8.79°C; minimum: 2.08±6.78°C).

Under 5 years of age, WBC was 11.19 (9.78-13.75), whereas it was 9.01 (7.69-11.04) above 5 years of age (p<0.001). Under 5 years of age, NLR was 1.08 (0.47-1.85), whereas it was 2.07 (1.30-3.55) above 5 years of age (p<0.001). Under 5 years of age, PLR was 76.72 (48.9-99.1), whereas it was 117.25 (83.76-159.46) above 5 years of age (p<0.001). Under 5 years of age, troponin was 9.25 pg/mL (2.8-19.8), whereas it was 2.4 (1.65-3.65) above 5 years of age (p<0.001). CK level in female patients was 100 U/L (79.5-131.5) and 145.5 (103-200) in male patients (p<0.001). Under 2 hour of admission time NLR was 1.51 (0.81-2.52), whereas it was 2.26 (1.28-3.75) above 2 hours (p=0.01) (Table 2).

Patients stratified by COHb levels into mild (MG), moderate (MoG), and severe (SG) groups demonstrated significant differences in key parameters. The SG group exhibited significantly lower admission pH values compared to milder cases (p=0.030) and markedly higher COHb levels (p<0.001). The SG exhibited significantly elevated inflammatory markers compared to MG and MoG, with median NLR (2.09 [IQR 1.24-3.54]; p=0.019) and PLR (106.2 [80.6-164.4]; p=0.032), confirming their association with disease severity. Climatic analysis revealed higher maximum temperatures in MG versus SG (p=0.032) (Table 3).

No significant associations were found between poisoning severity and age (p=0.278), gender (p=0.433), nationality (p=0.432), admission season (p=0.413), time-to-admission (p=0.910), or wind direction (p=0.768). Etiological analysis revealed distinct exposure patterns:

stove-related poisonings accounted for only 8.9% of SG cases, compared to 66.7% for natural gas and 60% for other sources (fire/hookah/exhaust; p=0.001). Clinical presentations varied significantly by severity: In the group with CNS symptoms, 28.6% of the cases were in the SG group, more than in the other groups (p=0.014). COHb levels showed no significant correlation with gender, age group, or time-to-hospitalization (Table 4).

Table 1. Sociodemographic characteristics of the patients who participated in the study		
Parameters	Subgroups	All patient, % (n) n=132
Age	0-5 year	28.8 (38)
	>5 year	71.2 (94)
Gender	Female	47 (62)
	Male	53 (70)
Nationality	Turkish	92.4 (122)
	Refugee	7.6 (10)
Hospital admission season	Spring	29.5 (39)
	Summer	2.3 (3)
	Fall	10.6 (14)
	Winter	57.6 (76)
Hospital admission day	Monday	10.6 (14)
	Tuesday	12.9 (17)
	Wednesday	24.2 (32)
	Thursday	12.1 (16)
	Friday	11.4 (15)
	Saturday	12.9 (17)
	Sunday	15.9 (21)
Admission hour	00-08	31.1 (41)
	08-16	38.6 (51)
	16-24	30.3 (40)
Location	Village	28.8 (38)
	District	25 (33)
	Center/city	46.2 (61)
Source	Stove	89.4 (118)
	Natural gas	2.3 (3)
	Others*	8.3 (11)
Incident admission time	0-2 hours	65.2 (86)
	>2 hours	35.8 (46)
Patient's arrival clinical symptoms	Respiration system ^μ	39.4 (52)
	CNS ^{**}	27.3 (36)
	GIS ^ε	33.3 (44)
* = Others: exposure to hookah, fire, car exhaust fumes, ^μ = shortness of breath, cough/choking ^{**} = CNS: central nervous system (headache, dizziness, drowsiness, confusion), GIS ^ε : gastrointestinal system (vomiting, nausea, abdominal pain)		

Table 2. Evaluation of hemogram, biochemistry and climate parameters between age, gender and incident admission time												
Parameters	Age*			Gender*			Incident admission time*					
	<5 year	>5 year	Z	p **	Female	Male	Z	p **	0-2 hour	>2 hour	Z	P**
Hemogram and biochemistry parameters												
WBC ¹ (x1000 mm ³)	11.19 (9.78-13.75)	9.01 (7.69-11.04)	-3.48	0.001	9.64 (7.64-11.31)	9.69 (8.22-12.92)	-1.06	0.288	9.66 (7.69-11.70)	9.45 (8.49-11.97)	-0.69	0.488
NLR ²	1.08 (0.47-1.85)	2.07 (1.30-3.55)	-3.63	<0.001	1.79 (1.03-3.42)	1.67 (0.90-2.88)	-0.83	0.404	1.51 (0.81-2.52)	2.26 (1.28-3.75)	-2.58	0.01
PLR ³	76.72 (48.9-99.1)	117.25 (83.76-159.46)	-3.85	<0.001	104.65 (77.65-164.03)	96.76 (64.83-123.82)	-1.59	0.111	97.13 (62.15-138.46)	107.91 (89.55-171.13)	-1.56	0.118
CK (U/L)	113 (87-169)	109 (90-169)	-0.23	0.812	100 (79.5-131.5)	145.5 (103-200)	-3.59	<0.001	109 (85-173)	116 (95-165)	-0.64	0.517
CK-MB (U/L)	31 (25.5-40.5)	24.5 (19.25-33.75)	-2.46	0.014	27 (22-33.25)	26 (20-41)	-0.365	0.715	27 (22-36)	26.5 (19-34)	-0.45	0.651
pH	7.37 (7.31-7.40)	7.35 (7.31-7.39)	-0.67	0.501	7.37 (7.32-7.40)	7.34 (7.31-7.38)	-1.62	0.104	7.35 (7.31-7.39)	7.36 (7.32-7.38)	-0.03	0.975
COHb	12.65 (6.07-20.75)	16.6 (10.35-23.75)	-2.09	0.036	14.1 (7.9-22.2)	15.9 (9.1-22.6)	-0.82	0.409	14.3 (7.6-23.95)	15.6 (10.37-20.82)	-0.48	0.631
Laktat	2.15 (1.6-3.22)	2 (1.60-2.70)	-0.92	0.357	2 (1.67-2.82)	2.05 (1.57-2.70)	-0.02	0.982	2.1 (1.6-2.72)	1.95 (1.50-2.75)	-0.58	0.560
Albumin (g/L)	43.8 (40.75-46.5)	44.8 (41.17-47.87)	-0.40	0.684	43.45 (41.17-46.55)	44.7 (41.2-48.35)	-0.59	0.550	43.1 (40.95-46.3)	44.65 (42.82-48.37)	-0.87	0.384
CRP ⁴ (mg/L)	0.32 (0.23-0.64)	0.56 (0.30-1.85)	-2.62	0.009	0.52 (0.28-1.38)	0.45 (0.25-1.47)	-0.29	0.767	0.49 (0.26-1.57)	0.44 (0.29-1.37)	-0.17	0.862
Troponin (pg/mL)	9.25 (2.8-19.8)	2.4 (1.65-3.65)	-3.77	<0.001	2.40 (1.55-6.12)	2.80 (1.90-5.00)	-0.75	0.454	2.5 (1.72-4.6)	3.2 (1.8-5.9)	-1.16	0.244
Climate parameters												
Max WS ⁴ (Knot)	10.3 (5.1-13.4)	7.95 (5.10-14.40)	-0.10	0.918	10.8 (6.45-14.4)	7.45 (5.10-13.02)	-1.77	0.076	7.7 (5.1-12.9)	10.3 (5.55-14.4)	-1.49	0.135
Mean WS ⁴ (Knot)	2.25 (1.37-3.8)	1.75 (1.17-3.72)	-0.73	0.463	2.4 (1.35-3.9)	1.4 (1.2-3.4)	-1.78	0.074	1.6 (1.2-3.7)	2.4 (1.37-4.05)	-1.46	0.142
Air pressure (mb)	903.45 (898.6-909.85)	904.8 (898.6-909.8)	-2.61	0.794	902.8 (898.6-907.8)	905.6 (901.05-910.10)	-2.14	0.032	905 (898.7-909.3)	903.3 (897.5-910.8)	-0.19	0.845
Mean temperature (°C)	2.25 (1.37-3.8)	8.50 (1-12.2)	-1.20	0.229	8.7 (1.0-12.2)	7.45 (-0.1-12.2)	-0.62	0.533	8.9 (0.52-12.25)	6.55 (0-10.9)	-1.17	0.241
Max temperature(°C)	11.2 (2.17-17.00)	12.3 (2.90-17.00)	-0.76	0.445	12.78 (2.82-17.0)	12.2 (2.82-17.00)	-0.15	0.880	12.3 (2.82-17.32)	10.9 (2.65-17.0)	-0.89	0.373
Min temprature (°C)	0.2 (-6.80-5.85)	3.05 (-1.10-7.62)	-1.81	0.069	2.4 (-0.8-7.6)	2.55 (-3.20-6.92)	-0.64	0.517	3.5 (-1.8-8.25)	0.2 (-1.17-5.42)	-1.54	0.123
*All values are given as median (25-75 Percentile), **.Mann-Whitney U test was performed; 1– white blood cell, 2– neutrophil lymphocyte ratio 3– platelet lymphocyte ratio 4– maximum wind speed 5– C reactive protein												

Table 3. Assessment of hemogram, biochemistry and climate parameters according to COHb classification

Parameters	Classification by COHb value			p*
	Mild	Moderate	Severe	
Hemogram and biochemistry parameters				
WBC ¹ (x1000 mm ³)	9.02 (7.08-10.76)	9.44 (8.07-11.99)	11.05 (9.23-13.00)	0.170
NLR ²	1.09 (0.46-2.92)	1.22 (0.6-2.47)	2.09 (1.24-3.54)	0.019
PLR ³	70.6 (46.7-111.4)	100.6 (62.0-123.4)	106.2 (80.6-164.4)	0.032
CK(U/L)	102 (86.25-177.25)	114.5 (88.75-171.0)	126 (91-180)	0.815
CK-MB (U/L)	20 (17.5-36.5)	27 (22-33)	34 (23-43)	0.181
pH	7.38 (7.33-7.41)	7.36 (7.31-7.39)	7.32 (7.29-7.37)	0.03
COHb	2.1 (1.5-2.7)	15.45 (10.55-20.65)	31.45 (27.25-34.2)	<0.001
Lactate	1.7 (1.25-2.3)	2 (1.6-2.72)	2.7 (1.8-3.45)	0.07
Albumin (g/L)	48.95 (44.6-49.0)	44.7 (41.7-47.9)	41.75 (39.17-44.62)	0.239
CRP ⁴ (mg/L)	0.41 (0.19-6.22)	0.51 (0.29-1.36)	0.45 (0.22-1.87)	0.879
Troponin (pg/mL)	2.5 (1.7-4.8)	2.9 (1.8-6.37)	2.1 (1.8-4.6)	0.712
Climate parameters				
Maximum WS ⁵ (Knot)	6.7 (6.2-10.8)	9 (5.1-14.4)	6.95 (5.1-11.55)	0.694
Average WS (Knot)	1.4 (1.0-2.4)	2.15 (1.27-3.8)	1.55 (1.4-3.97)	0.203
Air pressure (mb)	904.7 (901.6-909.3)	903.95 (898.6-910.1)	905.6 (898.3-909.7)	0.709
Average temperture (°C)	9.0 (7.4-12.3)	6.55 (-0.4-12.2)	10.3 (2.72-12.2)	0.198
Maximum temperture (°C)	14.2 (13.05-19.0)	12.3 (8.5-17.0)	10.8 (1.9-17.0)	0.032
Minimum temperture (°C)	3.5 (3.1-8.1)	0.45 (-3.2-6.55)	1.15 (-0.67-8.6)	0.103
*: All values are given as median (25-75 Percentile) and Kruskal-Wallis test was performed; 1– white blood cell, 2– neutrophil lymphocyte ratio, 3– platelet lymphocyte ratio, 4– C reactive protein				

*: All values are given as median (25-75 Percentile) and Kruskal-Wallis test was performed; 1– white blood cell, 2– neutrophil lymphocyte ratio, 3– platelet lymphocyte ratio, 4– C reactive protein

Table 4. Relationship between age, source of poisoning, time of event-admission and gender factors according to COHb value classification

Features		Severe (COHb>25) n (%)*	Moderate (COHb: 25-5) n (%)	Mild (COHb<5) n (%)	p
Age	0-5 year	3 (2.4)	26 (20.8)	7 (5.6)	0.278
	>5 year	15 (12)	64 (51.2)	10 (11.2)	
Source	Stove	10 (8.9)	87 (77.7)	15 (13.4)	0.001
	Natural gass	2 (66.7)	0 (0.0)	1 (33.3)	
	Others [†]	6 (60.0)	3 (30.0)	1 (10.0)	
Incident submission time	0-2 hour	15 (12)	54 (43.2)	12 (9.6)	0.144
	>2 hour	3 (2.4)	36 (28.8)	5 (4)	
Gender	Female	6 (4.8)	45 (36)	8 (7.2)	0.433
	Male	12 (9.6)	45 (36)	9 (6.4)	
Clinical symtoms	Respiration	4 (8.5)	32 (68.1)	11 (23.4)	0.014
	CNS**	10 (28.6)	24 (68.6)	1 (2.8)	
	GIS [‡]	5 (11.6)	33 (76.7)	5 (11.6)	

*: n (%); n=number, %: percentile, [†]Others: exposure to hookah, fire, car exhaust fumes; **=CNS: central nervous system (headache, dizziness, drowsiness, confusion), GIS[‡]: gastrointestinal system (vomiting, nausea, abdominal pain)

DISCUSSION

In this study, the relationship between pediatric cases of CO poisoning and systemic/immunoinflammatory markers and climate parameters was evaluated. Under 5 years of age, NLR was 1.08 (0.47-1.85), whereas it was 2.07 (1.30-3.55) above 5 years of age (p<0.001). Under

2 hour of admission time NLR was 1.51 (0.81-2.52), whereas it was 2.26 (1.28-3.75) above 2 hours (p=0.01). Severe Co poisoning appeared to be more common in the group with CNS findings (p=0.014). In relation to these data, a study conducted in Türkiye in 2013 (10) showed that symptoms were more severe in adolescents than in younger patients. A prospective study by Yalçın

et al. (11) demonstrated that an NLR value above 4 was significantly associated with the development of delayed neuropsychiatric syndrome (DNS), with an area under the curve (AUC) of 0.828, sensitivity of 78.2%, and specificity of 75.5 ($p < 0.001$). These findings support the potential use of NLR as a low-cost, accessible biomarker not only for evaluating acute disease severity but also for identifying children at higher risk of long-term complications. When interpreted alongside patient age, time to hospital admission, and symptom presentation, NLR may enhance early risk assessment and guide management strategies in pediatric CO poisoning cases.

Our study found no statistically significant association between gender and poisoning severity ($p = 0.433$). This finding aligns with existing literature reporting either comparable or slightly higher incidence rates among males (12,13). This likely reflects gender-specific exposure patterns rather than biological factors, as males in our region more frequently engage in high-risk activities like vehicle maintenance and outdoor combustion-related work. The lack of statistical significance despite numerical male predominance suggests that while exposure opportunities may vary by gender, clinical outcomes do not. These findings emphasize the need for prevention strategies targeting specific high-risk activities rather than demographic groups.

Our findings demonstrate a pronounced seasonal trend in CO poisoning incidence, with the majority of cases occurring during winter months (particularly in February) mirroring epidemiological patterns observed across diverse geographical regions. This temporal distribution aligns consistently with studies from Saudi Arabia (12), China (14) where 70% of cases clustered in winter months. The robust cross-cultural reproducibility of this phenomenon underscores its fundamental linkage to behavioral and environmental factors rather than regional peculiarities. The winter predominance reflects a confluence of risk determinants: heightened reliance on combustion-based heating systems, increased indoor confinement with inadequate ventilation, and the combustion inefficiency of fuels under low-temperature conditions. Particularly noteworthy is the February peak in our cohort, which may correlate with both the seasonal temperature nadir and cultural practices such as prolonged indoor heating during traditional winter periods. These observations collectively substantiate that CO poisoning represents not merely a clinical entity, but a socioclimatic phenomenon where environmental determinants interact with human behavioral patterns to create predictable risk windows. This evidence reinforces the imperative for targeted public health interventions including community education on ventilation practices and heating system maintenance to be intensified during these high-risk periods.

Our laboratory findings revealed a distinct biochemical progression associated with worsening clinical severity, characterized by elevated WBC counts, COHb, and lactate levels, coupled with decreasing pH, partial pressure

of carbon dioxide (PCO₂), and oxygen (PaO₂). This constellation of abnormalities paints a comprehensive picture of the dual pathological mechanisms underlying severe CO intoxication: Firstly, profound tissue hypoxia resulting from CO's competitive binding to hemoglobin, and secondly, a consequent systemic inflammatory response. The marked lactate elevation (2.7 [1.8-3.45] mmol/L in severe cases) serves as a particularly sensitive indicator of cellular hypoxia, reflecting the shift to anaerobic metabolism when oxygen delivery becomes critically impaired. These findings align precisely with the work of Keleş et al. (15), who similarly demonstrated the strong predictive value of hyperlactatemia in assessing poisoning severity. The concordance between our results and established literature not only validates our methodological approach but also reinforces lactate's role as a key biomarker for both diagnostic and prognostic evaluation in CO poisoning. Furthermore, the observed leukocytosis and acid-base disturbances suggest that secondary inflammatory cascades significantly contribute to the pathophysiology, potentially explaining why some patients develop delayed neurological sequelae despite normalization of COHb levels. This biochemical profile underscores the importance of monitoring both oxygenation parameters and inflammatory markers in the acute management of CO intoxication.

Our study demonstrated significantly higher NLR and PLR ratios in severe CO poisoning ($p = 0.019$ and 0.032 , respectively), consistent with findings by Bağcı et al. (7), who reported similar increases in these inflammatory indices with worsening severity. NLR and PLR, derived from routine complete blood counts, have emerged as valuable systemic immune-inflammation markers (SII) for assessing disease progression in pediatric populations (6). Their rapid availability, cost-effectiveness, and widespread accessibility make them particularly useful in emergency settings. The strong association between elevated NLR/PLR and CO poisoning severity suggests these ratios may serve as early, practical biomarkers to guide clinical decision-making, especially in resource-limited environments where advanced diagnostics may be unavailable.

Our study revealed that higher maximum air temperatures were associated with milder CO poisoning cases ($p = 0.032$), aligning with global observations that colder climates elevate poisoning risk (8,16,17). Notably, research from Taiwan quantifies this relationship, demonstrating a 10% reduction in CO poisoning risk per 1°C temperature increase (17). While our meteorological data—limited to daily averages rather than real-time measurements—recluded precise temporal correlations, the consistent inverse trend between temperature and poisoning severity persists. This phenomenon likely stems from behavioral adaptations to cold weather: increased indoor heating, reduced ventilation, and prolonged occupancy in enclosed spaces, all of which exacerbate CO accumulation. These findings underscore temperature as a modifiable

environmental risk factor, reinforcing the need for targeted public health interventions during colder months.

Strength and Limitations

This study advances the understanding of CO poisoning in pediatric populations by integrating both biochemical markers and climate parameters a novel approach that extends beyond the conventional focus on laboratory values prevalent in prior research within our region. The inclusion of meteorological data provides a more comprehensive assessment of environmental risk factors, offering valuable insights for region-specific prevention strategies. However, several limitations must be acknowledged. The single-center design may restrict generalizability, while the modest sample size limits the power to detect subtler associations. Additionally, the reliance on daily climate averages rather than real-time measurements introduces potential temporal variability in exposure assessment. Future multicenter studies with larger cohorts and granular environmental data would help validate these findings and further elucidate the interplay between climatic factors and CO poisoning severity.

CONCLUSION

This study provides valuable insights into the relationship between systemic inflammatory markers (NLR, PLR), climatic factors, and the severity of pediatric CO poisoning. The findings demonstrate that elevated NLR and PLR ratios are strongly associated with disease severity, reinforcing their potential as accessible, cost-effective prognostic tools in emergency settings. Furthermore, the inverse correlation between maximum temperature and poisoning severity aligns with existing literature, highlighting the role of environmental conditions in modulating exposure risk. The study's results contribute meaningfully to the understanding of CO poisoning pathophysiology and risk stratification.

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Machine Learning-Driven Metabolomic Biomarker Discovery for PCOS: An Interpretable Approach Using Random Forest and SHAP

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Abstract

Aim: This study aimed to predict Polycystic Ovary Syndrome (PCOS) using follicular fluid metabolomic data and the Random Forest algorithm, and to interpret the contributions of the most influential metabolites using SHapley Additive exPlanations (SHAP) analysis.

Material and Method: An untargeted metabolomic dataset of follicular fluid from 35 PCOS patients and 37 age-matched controls was utilized. The dataset was partitioned into 70% training and 30% testing subsets using stratified sampling. A Random Forest algorithm was employed, with hyperparameter optimization performed using RandomizedSearchCV. Model performance was evaluated using accuracy, sensitivity, specificity, F1 score, balanced accuracy, and Brier score. SHAP analysis was then applied to interpret the model's predictions and identify key contributing metabolites.

Results: The Random Forest model achieved robust classification performance, with an accuracy of 0.86, sensitivity of 0.82, specificity of 0.91, F1 score of 0.86, balanced accuracy of 0.85, and a Brier score of 0.13. SHAP analysis identified L-Histidine, L-Glutamine, and L-Tyrosine as the top three most influential metabolites. Specifically, decreased levels of L-Histidine and L-Tyrosine, and elevated levels of L-Glutamine, were associated with an increased risk of PCOS.

Conclusion: Our findings demonstrate the potential of integrating machine learning with explainable AI to accurately predict PCOS based on metabolomic profiles. The identified metabolites, particularly alterations in amino acid metabolism, offer novel insights into the metabolic underpinnings of PCOS and highlight their promise as diagnostic biomarkers, paving the way for more precise and interpretable diagnostic strategies.

Keywords: Polycystic ovary syndrome, metabolomics, random forest, shapley additive explanations, biomarkers

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, affecting approximately 10–15% of women of reproductive age. It is a complex, heterogeneous, and multifactorial condition (1,2). The key clinical features of PCOS include oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology. Additionally, PCOS is frequently associated with metabolic abnormalities such as insulin resistance, dyslipidemia, type 2 diabetes, and increased cardiovascular risk (3,4). Due to its variable clinical presentation and underlying biological mechanisms, PCOS is increasingly recognized not as a single disease but as a spectrum of different phenotypes (5). Recent studies have suggested that PCOS results from an interplay between genetic predisposition, environmental influences, and lifestyle

factors, involving hormonal, metabolic, and inflammatory pathways (6). Traditional biomarkers used for the diagnosis and classification of PCOS are often insufficient to capture this heterogeneity, complicating early diagnosis and the development of personalized therapeutic strategies. In this context, metabolomics- as a systems biology approach- has emerged as a powerful tool for identifying novel biomarkers and uncovering the metabolic subtypes of PCOS (7). Metabolomic studies have revealed significant alterations in energy metabolism, amino acid profiles, lipid metabolism, and oxidative stress pathways in individuals with PCOS (8,9).

However, analyzing and interpreting such high-dimensional and complex data requires advanced analytical approaches beyond conventional statistical methods. Machine learning (ML) algorithms, particularly ensemble

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methods like Random Forest, have demonstrated strong performance in classification tasks and are increasingly applied to disease prediction using metabolomic data (10). The Random Forest algorithm is especially valuable in biomarker discovery due to its embedded feature selection and resistance to overfitting (11). Nevertheless, the interpretability of these complex models is of paramount importance in biomedical applications to ensure their clinical trustworthiness. In this regard, SHapley Additive exPlanations (SHAP) has become a widely used method for interpreting ML model predictions. SHAP allows for quantifying and visualizing the individual contribution of each feature to a given prediction, thereby enhancing model transparency and facilitating biological interpretation (12,13).

In this study, we aimed to predict PCOS using metabolomic data and the Random Forest algorithm, and to subsequently interpret the contribution of the most influential metabolites using SHAP analysis. This approach seeks to provide an accurate and interpretable diagnostic model while also offering novel insights into the metabolic underpinnings of PCOS.

MATERIAL AND METHOD

Dataset

We utilized an untargeted metabolomic dataset of follicular fluid from 35 PCOS patients and 37 age-matched controls (14). Ethical review and approval were not required for this study, in accordance with institutional requirements and national legislation, as the analyses were performed using an open-access dataset. This dataset provides comprehensive metabolite profiles and sample metadata under CC BY 4.0 license. In the PCOS group (n=35), the majority of participants (n=29, 82.9%) exhibited prolonged irregular menstrual cycles, categorized as “Irregular (longer)”, while a smaller proportion (n=6, 17.1%) were diagnosed with oligomenorrhea.

Random Forest–Based Machine Learning Modeling Process

The dataset was partitioned into training (70%) and testing (30%) subsets using stratified sampling to preserve class distribution. Random Forest, an

ensemble learning algorithm, was employed due to its robustness and ability to handle high-dimensional data with complex interactions. It constructs multiple decision trees on bootstrap samples of the training data, each considering a random subset of features, which helps reduce overfitting and improve generalization. Hyperparameter optimization for the Random Forest model was performed using RandomizedSearchCV with 10 iterations and 5-fold cross-validation (15,16). The optimized model demonstrated strong classification performance, evaluated by various metrics including accuracy, sensitivity (recall), specificity, F1 score, balanced accuracy, and Brier score. To enhance model interpretability and elucidate the decision-making process, SHAP values were calculated. SHAP is a model-agnostic interpretability technique based on cooperative game theory that quantifies the contribution of each feature to individual predictions. This approach allowed the identification and visualization of the most influential metabolites involved in the prediction of PCOS, providing valuable biological insights and supporting the clinical applicability of the model (17).

Statistical Analysis

Data were summarized as mean±standard deviation or median (interquartile range; IQR). Normality was assessed separately for each group using the Shapiro-Wilk test. For variables meeting the normality assumption, group differences were evaluated using the independent two-sample t-test, while variables not meeting the assumption were analyzed with the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant. Data analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (18) and the Python programming language (19).

RESULTS

The dataset used in this research consists of a total of 72 patients, 35 PCOS (48.6%) and 37 (51.4%). The mean age of all patients is 30.2±3.9 years and the median age is 29 (23-41). Table 1 presents the baseline demographic features of individuals in the PCOS and control groups.

Table 1. The comparison of demographic characteristics between PCOS and control groups					
	Group				p-value
	Control (n=37)		PCOS (n=35)		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Age (years)	31.11±4.18	31 (5.5)	29.31±3.38	29 (3)	0.040*
Height (m)	1.62±0.04	1.63 (0.05)	1.61±0.05	1.6 (0.07)	0.213**
Weight (kg)	57.71±7.83	55 (13.5)	58.77±8.61	60 (10)	0.619**
BMI (kg/m²)	22.07±2.84	21.99 (4.8)	22.73±2.99	22.15 (4.4)	0.434*
Serum testosterone (ng/ml)	0.41±0.1	0.45 (0.19)	0.54±0.21	0.5 (0.32)	0.007*
SD: standard deviation, IQR: interquartile range, PCOS: polycystic ovary syndrome, BMI: body mass index; *: Mann-Whitney U; **: Independent sample t-test					

The Random Forest algorithm applied to the metabolites obtained from the metabolomic analyses yielded the following performance metrics: accuracy=0.86, sensitivity (recall)=0.82, specificity=0.91, F1 score=0.86, balanced accuracy=0.85, and Brier score=0.13. These results indicate that the model achieved a high level of predictive performance, with a good balance between sensitivity and specificity, suggesting its potential utility in distinguishing individuals with PCOS from controls based on metabolomic profiles. Following SHAP analysis to enhance model interpretability, the top 3 most influential metabolites contributing to the classification were identified as L-Histidine, L-Glutamine, and L-Tyrosine, highlighting the potential metabolic signatures associated with PCOS (Figure 1). Table 2 presents the distribution and statistical differences of the top 3 key metabolites identified by the model across the groups. The distribution and directionality of feature contributions to the model's predictions were further visualized using a SHAP beeswarm plot (Figure 2), which illustrates the impact of each metabolite on individual predictions and highlights their relative importance across the dataset.

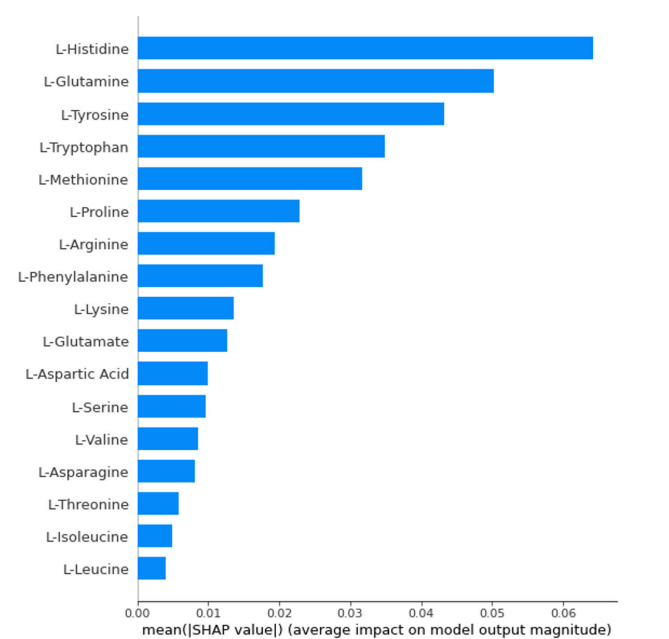


Figure 1. The metabolites contributing to the classification of PCOS versus control individuals, as identified through SHAP analysis

Table 2. Comparison of the distributions and statistical differences of the top 10 most important metabolites across the relevant groups					
	Group				p-value
	Control		PCOS		
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
L-Histidine	276826.07±61826.56	259220.76 (161017.47-432697.39)	229731.58±32052.18	230248.32 (167998.47-314654.97)	<0.001*
L-Glutamine	143904.12±22185.97	145987.85 (100208-179231.45)	171716.71±33932.91	166242 (127857-287643)	<0.001*
L-Tyrosine	18593.45±4130.27	17175.95 (13129.78-29317.8)	15693.43±2754.86	15805.95 (11079.54-21710.02)	0.005*
SD: standart deviation, IQR: interquartile range, PCOS: polycystic ovary syndrome; *: Mann-Whitney U					

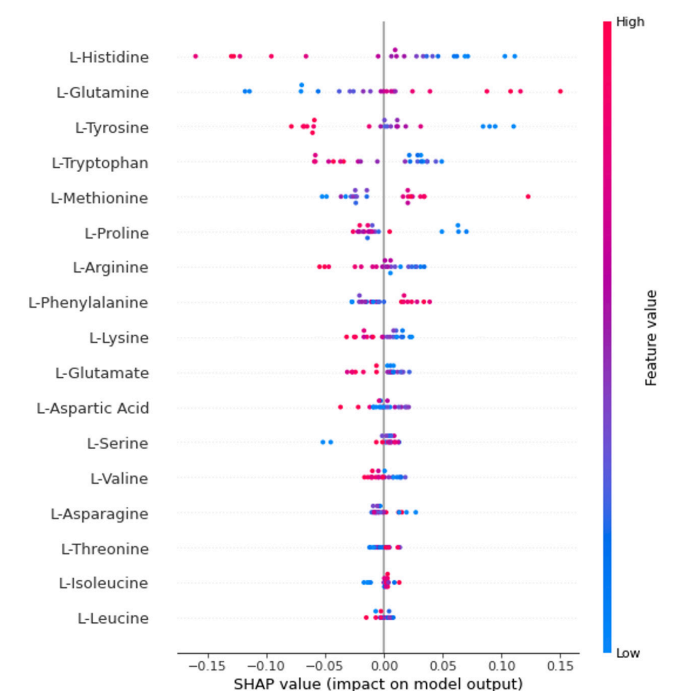


Figure 2. SHAP beeswarm plot illustrating the distribution and directionality of feature contributions to the model's predictions. Each point represents a single sample, showing the impact of individual metabolites on prediction outcomes and highlighting their relative importance across the dataset

DISCUSSION

PCOS is a complex endocrine disorder that is commonly observed in women of reproductive age and is characterized by heterogeneous clinical manifestations. Although the exact pathophysiology of PCOS has not been fully elucidated, insulin resistance, hormonal imbalances, and chronic inflammation are known to play central roles in its development. In recent years, multi-omics approaches and high-dimensional biomarker data have gained increasing importance in efforts to better understand the biological basis of PCOS. In this context, machine learning and artificial intelligence techniques have emerged as powerful tools for identifying meaningful patterns and potential biomarkers from large-scale metabolomic datasets (20). Supporting this perspective, Nsugbe (2023) proposed an AI-driven clinical decision support system for the early diagnosis and staging of PCOS. The study addressed common limitations in the field, such as class imbalance in training data, by applying synthetic oversampling (SMOTE) to the widely used Kaggle PCOS dataset. Ten machine learning models were evaluated, and nonlinear support vector machine (SVM) variants-particularly Cubic and Medium Gaussian SVMs-demonstrated the highest classification performance. Notably, the study extended beyond

binary classification to include a probabilistic inference system capable of distinguishing early and advanced stages of the condition. These findings highlight the potential of AI not only for accurate PCOS diagnosis but also for informing proactive, stage-specific clinical management strategies (21). Supporting this, Elmannai et al. (2023) developed a comprehensive PCOS prediction framework combining optimized feature selection and explainable AI (XAI) methodologies. Their study employed multiple machine learning algorithms, including logistic regression, random forest, SVM, and XGBoost, optimized via Bayesian search, and addressed class imbalance using a hybrid SMOTE-ENN strategy. Notably, the stacking ensemble model incorporating Recursive Feature Elimination (RFE) achieved 100% accuracy in the 80:20 data split and maintained high performance across metrics (ACC=98.87%, PRE=98.00%, REC=98.87%, F1=98.89%) in 70:30 splitting. In addition to predictive success, the study emphasized model transparency by integrating both global and local explanation techniques, demonstrating the importance of features such as follicle number and hormone levels. These findings affirm the growing utility of AI-based systems not only for accurate PCOS detection but also for interpretable, reliable, and individualized risk assessment (21). In this study, a Random Forest classification model based on metabolomic data was developed to identify potential biomarker metabolites for the diagnosis of PCOS, and the model's decision mechanisms were interpreted using SHAP analysis. The Random Forest model demonstrated a robust performance in distinguishing PCOS from control samples based on metabolomic data, with an accuracy of 0.86, sensitivity of 0.82, specificity of 0.91, F1 score of 0.86, balanced accuracy of 0.85, and a Brier score of 0.13. SHAP analysis was employed to interpret the model's decision-making process and to identify key metabolites contributing to the classification. Among all features, L-Histidine, L-Glutamine, and L-Tyrosine emerged as the top three most influential metabolites. Notably, decreased levels of L-Histidine and L-Tyrosine were associated with an increased risk of PCOS, while elevated levels of L-Glutamine were similarly linked to a higher PCOS risk. These findings suggest that specific alterations in amino acid metabolism may play a crucial role in the pathophysiology of PCOS and highlight their potential as diagnostic biomarkers. SHAP analysis identified L-Histidine, L-Glutamine, and L-Tyrosine as the top three metabolites influencing PCOS classification. Decreased plasma L-Histidine levels in PCOS have been consistently observed in multiple studies, likely reflecting its role as an antioxidant consumed under oxidative stress, with histidine showing high diagnostic power (AUC=0.90) in adipose tissue and plasma samples. Elevated L-Glutamine levels have also been reported in both fasting adolescent PCOS patients ($p=0.04$) and DHEA-induced PCOS rat models; in the latter, supplementation modulated inflammation, oxidative stress, insulin resistance (HOMA-IR) and LH levels (22-24). In our model, increased L-Glutamine was associated with higher PCOS risk,

aligning with its implication in metabolic dysregulation. L-Tyrosine typically shows increased concentrations in PCOS follicular fluid and exhibits positive correlations with androgen levels. Interestingly, our model indicated that reduced L-Tyrosine corresponded to elevated PCOS risk—a finding that diverges from existing literature and might be explained by differences in sample type, phenotypic subgroups, or the model's interpretative framework. Taken together, these results underscore the pivotal role of amino acid metabolism in PCOS pathophysiology and support further investigation of these metabolites as candidate diagnostic biomarkers. Overall, this study demonstrates the potential of integrating machine learning with explainable AI to uncover metabolite-based biomarkers, offering new insights into the metabolic underpinnings of PCOS and paving the way for more precise, interpretable, and personalized diagnostic strategies.

CONCLUSION

The findings of this study demonstrated that the integration of machine learning with explainable AI can provide accurate and interpretable diagnostic models for PCOS. The Random Forest model showed high classification performance, while SHAP analysis revealed that alterations in amino acid metabolism—particularly involving L-Histidine, L-Glutamine, and L-Tyrosine—play a significant role in distinguishing PCOS from controls. These findings highlight the potential of metabolomic biomarkers for improving diagnostic accuracy and deepening our understanding of the metabolic mechanisms underlying PCOS. Further validation in larger, independent cohorts is warranted to confirm the clinical utility of these metabolites and support their translation into personalized diagnostic strategies.

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Examination of 25-Hydroxyvitamin D Levels in Patients With Benign Positional Paroxysmal Vertigo

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Abstract

Aim: Benign paroxysmal positional vertigo (BPPV) is a prevalent cause of vertigo and dizziness. This study aimed to evaluate serum 25-hydroxyvitamin D [25(OH)-D] levels in patients diagnosed with posterior canal BPPV (PCBPPV) who presented to our clinic with dizziness complaints and healthy individuals without dizziness, and to investigate the association between low serum 25(OH)-D levels and BPPV.

Material and Method: Between January 2022 to March 2023, 50 patients (25 females, 25 males) with PCBPPV and 50 healthy controls (24 females, 26 males) without dizziness were enrolled. Serum 25(OH)-D levels of both groups were compared.

Results: Serum 25(OH)-D levels were significantly lower in the BPPV group compared to the control group ($p=0.031$). Serum 25(OH)-D levels were 20ng/mL or below in 37 patients (74%) in the patient group (mean: 14.25 ± 3.90), while this was observed in 28 individuals (56%) in the control group (mean: 15.94 ± 2.19).

Conclusion: Patients with BPPV exhibited significantly lower 25(OH)-D levels than healthy controls. These findings suggest that assessing vitamin D deficiency in BPPV patients may provide valuable insights into disease mechanisms and guide clinical management. Low 25(OH)-D levels appear to contribute to BPPV development.

Keywords: Benign positional paroxysmal vertigo, vitamin D deficiency, semicircular canals

INTRODUCTION

Vertigo is typically described as an internal sensation. Approximately 8-9% of patients diagnosed with Benign paroxysmal positional vertigo (BPPV), with an annual prevalence reported to be around 1.4-1.6% (1). Characterized by sudden, seconds-long positional vertigo attacks, BPPV is typically triggered by head movements. As it originates from the peripheral vestibular system, the vertigo attacks are considered "benign" since they do not stem from the central vestibular system. The severity of attacks varies from mild to severe across individuals. In addition to common symptoms, untreated or recurrent resistant BPPV patients may experience postural instability and a persistent sensation of vertigo. These patients often report that vertigo attacks can persist for days, weeks, months, or even years.

Under normal conditions, it is thought that otoconia become dislodged, are absorbed, and are continuously renewed. Sleeping is an etiological factor for BPPV. One study found a relationship between sleep position and recurrent BPPV (2). The patient's age can be a contributing factor to idiopathic BPPV. It is known that the incidence of BPPV increases with age among patients with vertigo.

BPPV triggered by head trauma can arise from a spectrum of injuries, ranging from mild incidents, such as flexion-extension (whiplash) injuries of the neck, to severe traumatic events involving the head. Typically, when BPPV is associated with head trauma, symptoms manifest within the first few days following the injury. However, these symptoms may be overlooked or misattributed due to the presence of more severe trauma-related injuries, such as concussions, fractures, or soft tissue damage,

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which often take precedence in clinical evaluations. The treatment response for BPPV caused by traumatic brain injury tends to be less robust compared to idiopathic BPPV, with patients potentially requiring more sessions of canalith repositioning maneuvers or experiencing prolonged symptom resolution. Despite this, remission rates for traumatic BPPV are generally comparable to those for idiopathic cases, indicating that while the initial response may be slower, long-term outcomes can be similar with appropriate management. Additionally, BPPV can occur in association with viral neuritis, a condition characterized by inflammation of the vestibular nerve, often following a viral infection. This selective involvement can lead to the dislodgement of otoliths, contributing to the development of BPPV symptoms in affected individuals. The interplay between viral neuritis and BPPV underscores the complex etiology of the condition, highlighting the need for thorough diagnostic evaluation to identify underlying causes and tailor treatment accordingly.

In addition to the previously mentioned factors, a variety of medical conditions and physiological states which include otitis media, which involves inflammation or infection of the middle ear, and sudden onset sensorineural hearing loss, can disrupt the vestibular system's function. Aerotitis, often associated with pressure changes during air travel or diving, may also predispose individuals to BPPV. Hematological disorders, such as polycythemia, characterized by an increased red blood cell count, can alter blood viscosity and potentially affect inner ear circulation, contributing to BPPV risk. Systemic conditions like hypertension and hyperlipidemia, which impact vascular health, are also recognized as risk factors, as they may compromise blood flow to the vestibular system. Additionally, dental surgeries, particularly those involving prolonged head positioning or trauma to the head and neck region, have been linked to the onset of BPPV. Sleep disorders, which can disrupt overall physiological balance and exacerbate stress on the vestibular system, may further increase susceptibility. Osteoporosis, a condition marked by reduced bone density, is another significant risk factor, particularly in older adults, as it may influence the structural integrity of the otoliths or surrounding bony structures in the inner ear. Low uric acid levels may impair the antioxidant defenses in the inner ear, potentially exacerbating vestibular dysfunction. Together, these diverse conditions highlight the multifactorial nature of BPPV and underscore the importance of a comprehensive clinical assessment to identify and address potential contributing factors.

The primary cause is the dissolution and displacement of otoliths. Otoliths are composite crystals located on the macular sensory epithelium. These crystals, formed in low-calcium (Ca^{2+}) endolymph, are divided into two regions. The core is low in calcium content, while the peripheral zone is rich in Ca^{2+} . There is a relationship between the concentration of free calcium in the endolymphatic fluid and otoliths. For these reasons, BPPV is thought to be associated with free calcium concentration. Vitamin D contributes to the regulation of otoconia by helping maintain calcium levels in the inner ear (3).

The pathophysiology of BPPV is explained by two mechanisms: "canalolithiasis," where otoconia dislodged from the utricular macula freely float within the affected semicircular canal (SSC), and "cupulolithiasis," where otoconia adhere to the cupula and it responds effectively to traditional maneuvers like Epley, Semont, and Brandt-Daroff.

Dislodged otoliths can either freely float within the SSC or adhere to the canal's ampulla. The free floating of otoliths within the canal is termed canalithiasis, while their adhesion to the canal's cupula is called cupulolithiasis. A single maneuver results in complete recovery in about 50-60% of cases, while repeated maneuvers increase this rate to over 90%.

BPPV, manifests through a range of distressing symptoms, including nausea, vomiting, nystagmus (involuntary eye movements), and dizziness, all of which are triggered by specific head movements or positional changes. These symptoms arise due to the displacement of otoliths (4). The condition's prevalence increases significantly with advancing age. Epidemiological data indicate that BPPV affects approximately 0.5% of individuals aged 18 to 39 years. The lifetime prevalence underscoring its growing burden in older populations (5). This age-related increase may be attributed to factors such as degeneration of the otolithic membrane, reduced bone density, or alterations in endolymphatic calcium levels, which can exacerbate otolith dislodgement. The recurrent and debilitating nature of BPPV symptoms highlights, particularly in elderly individuals who may face additional challenges due to comorbidities or reduced mobility.

BPPV occurs more frequently in women, with the majority of cases having no identifiable cause (6). While it is primarily an idiopathic condition affecting the inner ear, it may also be caused by head injuries. Women are impacted at a rate approximately twice that of men (7). BPPV is more prevalent in postmenopausal women compared to other individuals (1). In 90% of cases, it is observed that the posterior canal is involved.

The symptoms of BPPV are believed to result from the movement of otoconia from the utricle or saccule (8). In osteoporosis, disruptions in both calcium and vitamin D metabolism are likely key factors in BPPV pathogenesis (9-11). The importance of otoconia mineralization in the SSCs has been indicated in previous studies. (3). Furthermore, vitamin D levels have been found to influence sensory receptors in the membranous labyrinth of the SSCs (12). In fact, vitamin D treatment can reduce recurrent BPPV episodes, with complete remission achieved in many cases following vitamin D therapy (13,14).

MATERIAL AND METHOD

This study is a retrospective case-control study conducted between January 2022 and March 2023 at the Ear Nose Throat and Internal Medicine Clinics of Afyonkarahisar State Hospital. Fifty patients diagnosed with PCBPPV who presented with dizziness complaints and 50 healthy controls with no history of dizziness in the past year were included in the study. Patients aged

18–80 years were enrolled. All patients underwent neuro-otological examinations. Individuals with abnormal neuro-otological exam results, BPPV affecting the horizontal or anterior canals, abnormal audiometric findings, a history of inner ear disorders, head trauma, prior peripheral vestibular conditions, ear surgery, chronic kidney, liver, cardiovascular, or autoimmune diseases, or those undergoing vitamin D supplementation for any chronic systemic condition were excluded.

The vertigo diagnosis in the included patients was confirmed through history and physical examination.

Venous blood specimens were collected from both the patient and control groups at their initial visit to measure 25-hydroxyvitamin D [25(OH)-D] levels. Serum 25(OH)-D levels above 20 ng/mL were considered normal, while levels below 20 ng/mL were considered deficient.

The study was confirmed by the Scientific Research and Publication Ethics Commission of Afyonkarahisar Health Sciences University (dated 04.10.2024, decision no. 2024/8) and the institutional permission was obtained from Afyonkarahisar State Hospital, where the research personnel are actively employed (dated 02.08.2024).

Data analysis was applied using SPSS (Statistical Package for the Social Sciences) version 22.0. The normality of developments in the data was assessed by testing Kolmogorov-Smirnov. For comparisons of means between two groups, the Independent Samples T-test was used. A p-value <0.05 was considered statistically significant.

RESULTS

The research involved 50 patients with a BPPV diagnosis and 50 healthy controls. The BPPV group was evenly split with 25 males (50%) and 25 females (50%), whereas the control group comprised 26 males (52%) and 24 females (48%) (Table 1).

Table 1. Distribution of participants by gender			
BPPV	Gender	N	%
Patient	Female	25	50
	Male	25	50
Control	Female	24	48
	Male	26	52
N: number, BPPV: benign positional paroxysmal vertigo			

The mean 25(OH)-D level in the control group (18.82±3.87) was higher than the patient group comparison (16.34±4.94). There was a significant relationship between BPPV and the change in serum 25(OH)-D levels (p=0.006) (Table 2).

Table 2. Relationship between BPPV disease status and vitamin D level					
BPPV		N	Average	Standard deviation	P
Vitamin D level (<20ng/mL)	Patient	37	14.25	3.90	0.031
	Control	28	15.94	2.19	
N: number, BPPV: benign positional paroxysmal vertigo					

The mean age of the BPPV patient group was 53.34±17.88, while that of the control group was 37.44±17.35.

In the patient group, 37 individuals (74%) had serum 25(OH)-D levels at or under 20 ng/mL, compared to 28 individuals (56%) in the control group. A statistically significant association was observed between BPPV and low serum vitamin D levels (<20 ng/mL) (p=0.031) (Table 3).

Table 3. Relationship between BPPV and decreased serum vitamin D level					
BPPV		N	Average	Standard deviation	P
Vitamin D level (<20ng/mL)	Patient	50	16.34	4.94	0.006
	Control	50	18.82	3.87	
N: number, BPPV: benign positional paroxysmal vertigo					

A statistically significant relationship was found between BPPV and age (p=0.00). The mean age of the patient group (53.34±17.88) was higher than that of the control group (37.44±17.35) (Table 4).

Table 4. Relationship between BPPV and age					
BPPV		N	Average	Standard deviation	P
Age	Patient	50	53.34	17.88	0.00
	Control	50	37.44	17.35	
N: number, BPPV: benign positional paroxysmal vertigo					

No statistically significant relationship was found between gender and BPPV (p=1.00). Of the females, 51% were patients, while 49% of males were patients (Table 5).

Table 5. Relationship between gender and the presence of BPPV disease						
			BPPV		Total	P
			Control	Patient		
Gender	Female	N	24	25	49	1.00
		%	49	51	100	
	Male	N	26	25	51	
		%	51	49	100	
Total	N		50	50	100	
	%		50	50	100	
N: number, BPPV: benign positional paroxysmal vertigo						

DISCUSSION

BPPV is frequently seen in the fields of neurology, otolaryngology and internal medicine. Various factors such as gender, ethnicity, body mass index, dietary habits, latitude, or seasonal variations can affect serum vitamin D levels (15,16).

Otoconia develop through the aggregation of calcium carbonate crystals around a glycoprotein stone. Their creation, growth, and dissolution are driven by active calcium metabolism within the vestibular otolith organs (17). Disruptions in calcium and vitamin D metabolism, as seen in bone disorders like osteoporosis and osteopenia, have been linked to the occurrence of BPPV (18). The compound 25(OH)-D interacts with receptors involved in calcium metabolism in the inner ear (19). A decrease in inner ear calcium levels leads to a reduction in otoconia numbers (20,21). Similarly, Talaat et al. found that low serum vitamin D levels were associated with BPPV development (22).

A meta-analysis by Yang et al. indicated that BPPV is associated with vitamin D deficiency (<20 ng/dL) (9). Low vitamin D levels are linked to osteoporosis, a risk factor for BPPV, and it is suggested that elevating serum 25-hydroxyvitamin D3 levels could reduce BPPV severity and recurrence (13). However, some studies argue that coexisting chronic conditions such as hypertension and diabetes mellitus, along with advanced age, female gender, osteoporosis risk, and water intake, complicate the investigation of vitamin D deficiency's independent effect on BPPV development (2).

Vitamin D lack is more extensive in patients with BPPV than in the common population. A study conducted in China reported that 62.1% of BPPV cases had low serum vitamin D levels (14). Shin et al. discovered that low serum vitamin D levels were a risk factor for BPPV repetition (23). A study in India reported a statistically significant difference ($p=0.001$) between idiopathic BPPV and low vitamin D concentrations (24). Pecci et al. from Italy showed that correcting hypovitaminosis was effective in reducing BPPV episodes (25). Our results were consistent with the aforementioned studies, suggesting that low serum vitamin D levels may be a cause of BPPV.

When examining the risk factors for vestibular vertigo, it is associated with female gender, age, depression, and various cardiovascular diseases. Particularly in geriatric individuals, the increased risk factors and difficulties in applying diagnostic tests make it challenging to evaluate vertigo and determine the potential cause of balance problems. Consistent with other studies in the literature regarding vitamin D, this study also suggests that vitamin D deficiency may be a risk factor for BPPV.

A recently published meta-analysis and review study reported that some chronic conditions risk factors for BPPV recurrence (26). Similarly, Zhu et al.'s study involving 1,012 BPPV patients indicated that chronic conditions may increase the recurrence rate of BPPV (27). Consistent

with other studies, this study also highlighted that vitamin D deficiency significantly increases BPPV recurrence within the first year ($p<0.05$). However, Kim et al. reported a significant association between reduced bone mineral density and BPPV occurrence, but found no association with BPPV recurrence (28).

A study involving 80 patients with idiopathic BPPV, consistent with our research, confirmed that low serum 25(OH)-D levels contribute to BPPV development. Furthermore, 25(OH)-D levels were notably lower in patients with recurrent BPPV compared to those without recurrence (23). In a separate study, 130 patients with idiopathic BPPV were matched with 130 controls by age and gender to evaluate bone mineral density and 25(OH)-D levels, revealing an participation between low 25(OH)-D levels and BPPV in males (26). Additionally, Parham et al. investigated 16 BPPV patients and 13 osteoporosis patients among postmenopausal women, comparing serum ionized calcium and 25(OH)-D levels, and identified a negative relationship between vitamin D levels and BPPV (29).

Calcium metabolism is a complex and dynamic physiological process that encompasses dietary absorption, hormonal regulation, bone storage, and renal excretion. This tightly regulated system ensures that calcium levels remain within an optimal range to support critical functions such as bone mineralization, muscle contraction, nerve transmission, and vestibular system integrity. PTH, secreted by the parathyroid glands, responds to low serum calcium by mobilizing calcium from bone stores, increasing renal calcium reabsorption, and stimulating vitamin D activation to boost intestinal calcium uptake. Together, these mechanisms maintain the delicate balance required for bone health and the proper functioning of the vestibular system, which relies on calcium for the structural integrity of otoliths in the inner ear. Disturbances in calcium metabolism, such as vitamin D deficiency, PTH dysregulation, or renal dysfunction, can lead to abnormal calcium levels in the endolymphatic fluid and potentially contribute to dissolution or displacement of otoliths. This disruption may exacerbate otolith dysfunction due to altered calcium dynamics, increasing the risk of vertigo attacks. These intricate interactions underscore the importance of maintaining balanced calcium metabolism to prevent conditions like BPPV and highlight the need for comprehensive evaluation of calcium-regulating pathways in patients presenting with vestibular symptoms

Karataş et al. found no notable correlation between BPPV and serum 25(OH)-D levels in their study (9,10). In our research, 55% of participants exhibited 25(OH)-D levels below the normal range, and serum 25(OH)-D levels were significantly reduced in BPPV patients compared to the control group.

Güler et al. observed no notable differences in age or gender between BPPV patients and the control group (30). In our study, the average age of the patient group (53.34 ± 17.88) was greater than that of the control group (37.44 ± 17.35),

and a statistically significant association was identified between BPPV and age.

Vitamin D levels are not routinely assessed in otolaryngology clinics for BPPV patients. As a result, some patients are unaware of whether they have a deficiency in this vitamin.

CONCLUSION

Our research has shown that the deficiency of the mentioned vitamins contributes significantly to the onset of BPPV. These findings suggest that insufficient vitamin D levels may play for pathogenesis of BPPV. This assessment may not only aid in confirming the diagnosis but also guide the development of personalized treatment strategies, such as vitamin D supplementation, to address deficiencies and potentially reduce the severity or recurrence of vertigo attacks. Furthermore, routine monitoring of vitamin D levels could serve as a prognostic tool, helping to predict the course of BPPV and identify patients at higher risk of recurrent episodes.

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Prediction of Mortality Using Hematological and Biochemical Markers in Pneumonia Patients Followed in the Intensive Care Unit: A Retrospective Observational Study

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Abstract

Aim: Pneumonia remains a leading cause of mortality among patients admitted to intensive care units (ICUs). The use of hematological and biochemical markers has gained increasing importance in enhancing the accuracy of diagnosis and prognosis. Biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-platelet ratio (NPR), and the C-reactive protein/albumin ratio, which are calculated using complete blood count parameters, may aid in assessing the severity of systemic inflammation and predicting mortality. Our study examined how NLR, PLR, NPR, and CRP/Albumin ratios affect mortality in ICU patients hospitalized with pneumonia.

Material and Method: This retrospective observational study was conducted at a single center and involved 163 patients diagnosed with pneumonia and admitted to the ICU between May 1, 2021, and March 31, 2025. Demographic data, mortality status, and laboratory parameters at admission were obtained from the hospital information management system. Based on hematological (hemoglobin, neutrophil, lymphocyte, platelet) and biochemical (CRP, albumin) data, NLR, PLR, NPR, and CRP/Albumin ratios were calculated. Patients were categorized into survivors and non-survivors according to 30-day outcomes, and the relationship between the biomarker levels and mortality was analyzed statistically.

Results: A cohort comprising 163 ICU patients diagnosed with pneumonia underwent evaluation, revealing a 30-day mortality rate of 35% (n=57) within this patient population. No significant differences in age or sex were observed between survivors and non-survivors ($p>0.05$). The CRP levels were significantly lower, while albumin and hemoglobin levels were significantly higher in the survivor group ($p<0.05$). The CRP/albumin ratio was significantly elevated in non-survivors ($p=0.001$). Although no statistically significant differences were found for NLR, PLR, and NPR between the groups, these markers tended to be lower in survivors.

Conclusion: According to the findings of our study, low hemoglobin and albumin levels, as well as high CRP levels and CRP/Albumin ratios, were associated with mortality. NLR, PLR and NPR were found to be high in survivors, although not statistically significant. The CRP/Albumin ratio stands out as a reliable biomarker for predicting mortality, whereas NLR, PLR, and NPR, despite their limited sensitivity, may be used as supportive parameters due to their high specificity.

Keywords: Pneumonia, C-reactive protein, neutrophil, lymphocyte, albumin

INTRODUCTION

Pneumonia, characterized by an acute infection of the pulmonary parenchyma, continues to be the most prevalent cause of infectious mortality globally. When diagnosing pneumonia, both clinical symptoms and laboratory and radiological findings are evaluated with a holistic approach (1). For this reason, the importance of evaluating laboratory parameters and clinical findings together in diagnosis and prognosis has increased.

Recent research has increasingly emphasized the diagnostic and prognostic utility of diverse biochemical markers in individuals afflicted with pneumonia (2). Complete blood count (CBC) is a routine laboratory method used in intensive care units (ICUs), offering a low-cost and accessible means of evaluating blood cells. Hematological parameters, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-platelet ratio (NPR), have

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been extensively demonstrated in numerous studies to function as biomarkers for systemic inflammation and infection across diverse diseases (3). In particular, NLR has been identified as an important prognostic biomarker in diseases such as diabetes mellitus, cardiovascular diseases, respiratory disorders and malignant neoplasms (4). Similarly, PLR has been utilized in assessing the severity of infectious diseases such as pneumonia and is also considered a marker of systemic inflammatory response and vascular thrombosis (5).

C-reactive protein (CRP) is a biomarker that exhibits elevated concentrations in response to inflammatory conditions, particularly infections and autoimmune diseases. Furthermore, in pathologies characterized by chronic inflammation, such as chronic obstructive pulmonary disease, notable increases in classic inflammatory markers, including CRP and erythrocyte sedimentation rate, alongside heightened levels of NLR and PLR, have been documented (6). Conversely, albumin functions as a negative acute-phase reactant, with reduced serum concentrations commonly observed during inflammatory states. Hypoalbuminemia is considered an independent prognostic marker associated with increased mortality in various clinical conditions (7). An elevation in the CRP/Albumin ratio has been shown to be more sensitive in predicting prognosis than an elevation in CRP or albumin levels (8,9).

Given the high mortality associated with severe pneumonia, timely prognostic evaluation is essential for implementing comprehensive and effective treatment strategies. In recent years, various biomarkers have been extensively studied in numerous clinical conditions due to their rapid, accurate, and cost-effective results. This study aims to evaluate the predictive value of NLR, PLR, and NPR along with the CRP/Albumin ratio, in forecasting mortality among patients admitted to the ICU with a diagnosis of pneumonia.

MATERIAL AND METHOD

This single-center retrospective study utilized data from 163 patients (65 females, 98 males) aged over 18 years who were admitted to the ICUs of Ordu University Training and Research Hospital with a diagnosis of pneumonia between May 1, 2021, and March 31, 2025. Data regarding patients' age, sex, length of hospital stay, mortality status, and laboratory results at admission were retrospectively retrieved from the hospital information management system.

For laboratory evaluations, samples were analyzed using a Cobas 8000 c 702 fully automatic biochemistry analyzer (Roche Diagnostics, Mannheim, Germany) for analysis of CRP and albumin levels.

Samples for hematological parameters (Hb, neutrophils, lymphocytes, platelets) were analyzed using the Sysmex XN-1000 fully automatic hematology analyzer (Sysmex Corporation, Kobe, Japan).

Systemic inflammation indices were computed using the following formulas based on admission laboratory

parameters: $NLR = \frac{\text{Absolute neutrophil count}}{\text{Absolute lymphocyte count}}$, $PLR = \frac{\text{Absolute platelet count}}{\text{Absolute lymphocyte count}}$, $NPR = \frac{\text{Absolute neutrophil count}}{\text{Absolute platelet count}}$.

Participants were stratified into two cohorts according to their 30-day clinical outcomes: survivors and non-survivors. Comparative analyses were conducted to evaluate differences in NLR, PLR, NPR, CRP, albumin levels, and CRP/albumin ratios between the two mortality groups.

The study protocol received approval from the Clinical Research Ethics Committee of Ordu University (Approval Date: April 11, 2025; Application No: BAEK 128; Decision No: 2025/118).

Statistical Analysis

All statistical evaluations were performed using MedCalc statistical software (version 20.009; Ostend, Belgium). Continuous variables were expressed as mean±standard deviation (SD), as well as median with interquartile ranges (25th–75th percentiles), while categorical variables were summarized as counts and percentages. Group differences for categorical data were assessed using the chi-square test.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate and compare the diagnostic performance of measured and calculated laboratory parameters in predicting pneumonia-related mortality. The Youden J index was used to identify optimal cutoff thresholds. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) were reported. A p-value <0.05 was considered indicative of statistical significance in all tests.

RESULTS

A total of 163 patients were enrolled in the study, comprising 65 females (39.9%) and 98 males (60.1%). Among the patient population analyzed, 57 patients (35.0%) died. Detailed demographic data and laboratory findings for all participants are presented in Table 1.

Table 1. Demographic characteristics and laboratory data of the patients		
Variables		Total patients (n=163)
Gender	Female, n (%)	65 (39.9)
	Male, n (%)	98 (60.1)
Age, Median (25p-75p)		77 (65-83)
Mortality	Non-survivor, n (%)	57 (35)
	Survivor, n (%)	106 (65)
NLR, Median (25p-75p)		7.2 (3.9-12.1)
PLR, Median (25p-75p)		203.3 (138-369)
NPR, Median (25p-75p)		0.03 (0.02-0.05)
CRP/Albumin, Median (25p-75p)		28.1 (9.5-56.3)
25p-75p: 25. persentil-75. persentil, SD: standard deviation, NLR: neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio, CRP: C-reactive protein, n: number		

There were no statistically significant differences between the survivor and non-survivor groups regarding

sex or age ($p=0.448$ and $p=0.304$, respectively). However, CRP levels were significantly lower in the survivor group, whereas albumin and hemoglobin (Hb) levels were notably higher ($p=0.028$, $p<0.001$, and $p=0.002$, respectively). The CRP-to-albumin ratio was also found to be significantly reduced in survivors ($p=0.001$).

When evaluating hematologic parameters, neutrophil, lymphocyte, and platelet counts did not show statistically significant differences between groups. Nonetheless, survivors tended to have lower neutrophil counts and relatively elevated lymphocyte and platelet levels. Similarly, inflammation-based indices (NLR, PLR, and NPR) did not differ significantly between groups, though lower values were observed among survivors ($p=0.095$, $p=0.791$, and $p=0.197$, respectively) (Table 2).

Table 2. Comparison of gender, age, measured and calculated laboratory parameters according to mortality status						
		Groups				
		Non-survivor		Survivor		P-value
		N=57		N=106		
Gender	Female, n (%)	25	43.9	40	37.7	0.448
	Male, n (%)	32	56.1	66	62.3	
Age (years), Median (25p-75p)		77	65.8-88.2	77	65-82	0.304
CRP (mg/L), Median (25p-75p)		136	49.3-213.2	85	26.5-150.6	0.028
Albumin (g/L), Median (25p-75p)		2.7	2.8-3.3	3.5	3.1-4	<0.0001
Hb (g/dL), Mean (SD)		10.5	2.32	11.6	2.08	0.002
Neutrophils (10 ³ /L), Median (25p-75p)		8.8	5.5-13	7.8	5.1-11.5	0.409
Lymphocytes (10 ³ /L), Median (25p-75p)		1.07	0.72-1.56	1.17	0.86-1.78	0.122
PLT (10 ³ /L), Median (25p-75p)		217	138-318	251	197-323	0.075
NLR, Median (25p-75p)		9.56	3.9-14.4	6.85	3.9-10.9	0.095
PLR, Median (25p-75p)		207	139-333	202	138-371	0.791
NPR, Median (25p-75p)		0.04	0.02-0.07	0.03	0.02-0.05	0.197
CRP/Albumin, Median (25p-75p)		42.3	13.9-79.1	22.4	7.8-47.1	0.001
NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio, CRP: C-reactive protein, n: number, Hb: hemoglobin, PLT: platelet						

In the ROC curve analysis conducted to assess the predictive value of calculated laboratory markers for pneumonia-related mortality, the optimal threshold for NLR was identified as 12.35, yielding a sensitivity of 37% and specificity of 84%. For PLR, the cutoff was 162.7, with corresponding sensitivity and specificity values of 72% and 39%. The optimal cutoff for NPR was found to be 0.063, with 32% sensitivity and 91% specificity.

Among all variables examined, only hemoglobin and the CRP/albumin ratio demonstrated statistically significant diagnostic accuracy for predicting mortality. The ideal threshold for Hb was <10.6 ($AUC=0.646$, $p=0.002$), while that for the CRP/albumin ratio was >50 ($AUC=0.660$, $p=0.001$), as shown in Table 3.

Table 3. Diagnostic values of laboratory parameters associated with mortality due to pneumonia							
	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P-value
Hb (g/dL)	≤ 10.6	56	70	50.0	74.7	0.646	0.002
CRP/Albumin	> 50	47	81	57.4	74.1	0.660	0.001
NLR	> 12.35	37	84	55.3	71.2	0.579	0.111
PLR	> 162.7	72	39	38.7	71.9	0.513	0.795
NPR	> 0.063	32	91	64.3	71.1	0.561	0.224
NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, NPR: neutrophil-to-platelet ratio, CRP: C-reactive protein, Hb: hemoglobin, PLT: platelet, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve							

DISCUSSION

Pneumonia is defined as an acute infectious process of the pulmonary parenchyma and is considered one of the leading causes of morbidity and mortality worldwide, being the most common infectious cause of death globally (10).

ICUs are hospital departments where critically ill patients are monitored and treated, often with high mortality rates. Among the critical factors influencing prognosis within this patient cohort, age stands out, with advanced age having consistently demonstrated a significant association with elevated mortality rates (11). Indeed, Kocaoğlu and Alatlı reported that the mean age of non-survivors was

statistically significantly elevated in comparison to that of survivors (12). Despite optimal treatment strategies, 30-day mortality in pneumonia has been reported to range between 10% and 12% (13). However, the mortality rate observed in our current study (34.9%) was significantly higher than that reported in the literature. This finding may be attributed to the fact that our study sample consisted mostly of elderly individuals.

Combining clinical findings with scoring systems offers important indicators for identifying pneumonia patients at risk. The use of such prognostic markers is increasingly favored both to predict disease progression and to guide timely and appropriate antibiotic therapy (14,15). With the increasing number of critically ill patients and consequently higher mortality rates, early identification of high-risk cases has become imperative, highlighting the growing need for alternative biomarkers.

As components of standard laboratory panels, neutrophil and lymphocyte counts provide valuable insight into inflammatory status (16). Inflammatory conditions often result in increased platelet activation and fragmentation, leading to elevated platelet counts (17).

NLR is a practical and effective biomarker that reflects systemic inflammation (18). Huang et al. reported that NLR serves as a reliable prognostic parameter in septic patients, with higher NLR levels correlating with worse outcomes (19). Consistent with these findings, our study also demonstrated elevated NLR levels in the non-survivor group. Infections trigger cytokine release, which subsequently stimulates bone marrow activity and promotes platelet production, thereby leading to increased PLR values (17,20). Both PLR and NPR have been reported to play important roles in predicting prognosis across various conditions, including community-acquired pneumonia, malignancies, and myocardial infarction (21,22). Supporting this, Kumar et al. and Altaş & Kızılkaya identified NLR and PLR as significant predictors of mortality, while Wang et al. emphasized NLR alone as a reliable prognostic indicator (17,23,24). Conversely, Çiğri et al. observed a significant association between NLR and pneumonia severity but reported no corresponding changes in PLR (25). Similarly, Kocaoğlu & Alatlı and Bıyıklı et al. concluded that PLR is not a sufficiently robust prognostic marker in ICU populations (12,26). In line with these observations, our study also found no statistically significant difference in PLR levels, although survivors exhibited comparatively lower values. NPR has likewise been associated with mortality in multiple studies (27,28). Consistent with the findings of Doğançıl et al., we observed elevated NPR levels in the non-survivor cohort (29).

Anemia is a common condition among ICU patients. Various randomized trials have associated low Hb values with poorer life quality outcomes (30). Similarly, our study found a significant relationship between low Hb levels and mortality, indicating that Hb should be considered a key prognostic parameter in ICU settings.

Elevated CRP concentrations are indicative of an unfavorable prognosis across a multitude of clinical conditions, encompassing, but not limited to, coronary artery disease, ischemic stroke, sepsis, and diverse malignant neoplasms (31). Among patients in critical care, albumin levels demonstrate an inverse relationship with mortality risk. When CRP's role in acute inflammation is taken into account alongside albumin's predictive value, their ratio may offer enhanced diagnostic sensitivity and specificity. Consistent with the literature, our study found that patients who died had lower albumin levels and higher CRP and CRP/albumin ratios (31). Several studies also support the prognostic value of this ratio (32,33). However, Hoşgün et al. found that this ratio was not a significant prognostic value in pneumonia-related mortality (34). The CRP/Albumin ratio is considered a stronger prognostic marker than any single parameter alone.

Evaluations of NLR cut-off values suggest that this index may possess prognostic utility in clinical practice. Altaş and Kızılkaya reported a threshold of 11.3, which yielded 81.3% sensitivity and 77.1% specificity (17). Similarly, Zhang et al. identified an optimal cut-off of 5.92 with prognostic relevance (35). In contrast, our study demonstrated that an NLR cut-off of 12.35 achieved 37% sensitivity and 84% specificity. Taken together, these results indicate that although elevated NLR values carry prognostic significance, the index alone may not be sufficiently robust as a screening tool.

Kumar et al. reported a PLR cut-off value of 235, yielding 63% sensitivity and 74% specificity in predicting mortality (23). Similarly, Altaş and Kızılkaya identified a cut-off of 227, with 67.2% sensitivity and 62.5% specificity (17). In our study, a lower PLR cut-off of 162.7 achieved 72% sensitivity but only 39% specificity. These findings indicate that although PLR demonstrates relatively high sensitivity, its specificity remains limited. Therefore, PLR may be valuable in excluding mortality risk; however, its standalone diagnostic utility appears restricted.

In the study by Akan & Bilgir, the average NPR in deceased patients was reported as 0.022 (27). In our study, an NPR value >0.063 showed the highest specificity among all parameters.

The limitations of the present study include its retrospective design and single-center setting, which collectively contributed to a relatively small sample size. To corroborate these findings, further prospective, multi-center studies involving larger patient populations are warranted.

CONCLUSION

Our findings suggest that high CRP/Albumin ratios and CRP levels and low albumin and Hb levels may serve as rapid and practical predictors of mortality in pneumonia patients. The combined evaluation of these parameters holds the potential to enhance the precision of mortality prediction and contribute significantly to the timely initiation of diagnosis and treatment. Taking

into account the cut-off values of laboratory tests may help clinicians to develop early treatment strategies. Although NLR, PLR, and NPR serve as useful markers of systemic inflammation, further comprehensive studies are required to validate their effectiveness and reliability in the general population and across diverse infectious etiologies.

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Comparison of Comorbid Diseases Between Early-Onset and Late-Onset Systemic Lupus Erythematosus; A Single Center Retrospective Experience

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Abstract

Aim: To examine the comorbidity profile of patients with systemic lupus erythematosus (SLE) and to evaluate differences in comorbidity burden between late-onset and early-onset SLE patients.

Material and Method: We retrospectively analyzed SLE patients who presented to the tertiary rheumatology clinic between February 2024 and February 2025. Patients were categorized by age at diagnosis into three groups: childhood-onset (<18 years), adult-onset (18–49 years), and late-onset (≥50 years). Comorbidities were systematically documented and compared across groups.

Results: 284 SLE patients were included, with a mean age at diagnosis of 37.2 (±11.2) years; 83.8% were female. Arterial hypertension was the most common comorbidity (23.9%). Of the patients, 27 (7.1%) had childhood-onset SLE, 176 (61.9%) had adult-onset, and 81 (28.5%) had late-onset SLE. Arterial hypertension (46.9% vs. 15.9% and 7.4%, $p_1=0.004$, $p_2=0.0021$) and osteoporosis (22.2% vs. 4.5% and 3.7%, $p_1=0.014$, $p_2=0.032$) were more common in the late-onset SLE. The childhood SLE had higher rate of autoimmune thyroid diseases (22.2%), although differences between groups were not statistically significant.

Conclusion: Comorbid conditions, such as arterial hypertension and osteoporosis are more prevalent in late-onset SLE patients. These comorbidities may complicate disease management and should be considered as part of a comprehensive treatment strategy to optimize outcomes in daily clinical practice.

Keywords: Systemic lupus erythematosus, comorbidity, late-onset systemic lupus erythematosus, arterial hypertension, osteoporosis

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that can present at various ages and manifests with diverse clinical subphenotypes (1). Although high morbidity and mortality due to severe organ involvement at diagnosis or during the disease course remain significant concerns, outcomes have improved considerably over the past five decades with the increased use of immunosuppressive therapies (2). Despite these advances, the comorbidities in SLE continues to influence treatment decisions and therapeutic success (3,4).

In addition to conventional risk factors, persistent inflammation related to SLE and the adverse effects of medications—particularly glucocorticoids—may predispose patients to the development of comorbid

conditions (5). These comorbidities are also associated with reduced quality of life and make disease activity more difficult to manage (6). Although comorbidity burden generally increases with age, it is noteworthy that childhood-onset SLE patients may also experience significant comorbidities (7-9). Previous studies have consistently shown higher comorbid conditions in late-onset SLE (10).

As a result, managing comorbid diseases has become an essential component of care in late-onset SLE, alongside disease-specific treatment. The objective of the present study was to examine the frequency and distribution of comorbidities by age at diagnosis in SLE patients followed at a tertiary rheumatology center over a one-year period.

CITATION

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MATERIAL AND METHOD

Selection of Patients

This was a retrospective, single-center study. We included SLE patients who presented to the Rheumatology Clinic at Gülhane Training and Research Hospital between February 2024 and February 2025. Patients were selected using International Classification of Diseases (ICD)-10 diagnosis codes from the hospital's electronic medical records. Individuals under the age of 18, those with repeated admissions, missing clinical data, or an unconfirmed diagnosis were excluded from the study. Only patients who met the revised 1990 American College of Rheumatology (ACR) SLE classification criteria were included. The study received ethical approval from the Institutional Review Board of Gülhane Training and Research Hospital, University of Health Sciences (Date: 06 May 2025; Decision number: 2025/272).

Clinical Information and Comorbidity Profile

Demographic and clinical data were retrieved from electronic medical system. Laboratory and autoantibody profiles were documented. Comorbid conditions were determined based on prior diagnoses, prescribed medications, and treatment history documented in the medical records. The following comorbidities were evaluated: arterial hypertension (HT), diabetes mellitus (DM), chronic kidney disease (CKD), autoimmune thyroid diseases, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD)/asthma, dyslipidemia, malignancy, osteopenia/osteoporosis, and avascular necrosis. The diagnoses of comorbid conditions were accurately documented, as were details of the patient's medical history, ICD-10 diagnosis codes, and prescribed medications.

Patients were categorized into three groups based on their age at diagnosis:

- Childhood-onset SLE (<18 years),
- Adult-onset SLE (18–49 years),
- Late-onset SLE (≥50 years) (11).

Statistical Analysis

The SPSS version 26.0 was used to perform for statistical analyses. Normality of variable distributions was assessed using both visual methods (histograms, normality plots) and analytical methods (Kolmogorov–Smirnov test). The chi-square test was used to compare and p-value <0.05 was considered statistically significant. One-way ANOVA and subsequent post hoc tests were used to compare groups affected by SLE and those with comorbid diseases.

RESULTS

284 patients with SLE were included in the study. The demographic and clinical characteristics of the patients were presented in Table 1. The mean age at diagnosis was 37.2 (±11.2) years, and 83.8% were female. The most common clinical manifestations were skin involvement (76.0%) and musculoskeletal involvement (69.7%). In total, 90.8% of patients had used hydroxychloroquine, and 58.8% had been treated with at least one immunosuppressive agent. Table 2 summarizes the comorbidities among all SLE patients.

Table 1. The demographic and clinical characteristics of patients with SLE	
Demographic and clinical findings	All SLE patients n=284
Age at diagnosis, (SD)	37.2 (11.2)
Gender, female, n (%)	238 (83.8)
Disease duration, (SD)	9.3 (3.2)
Skin involvement, n (%) (acute cutaneous lupus, subacute cutaneous lupus, discoid lupus erythematosus, and lupus panniculitis)	216 (76.0)
Musculoskeletal involvement, n (%)	198 (69.7)
Alopecia, n (%)	99 (34.8)
Oral ulcers, n (%)	58 (20.4)
Renal involvement, n (%)	62 (21.8)
Hematological involvement, n (%)	44 (15.4)
Cardiac involvement, n (%)	4 (1.4)
Gastrointestinal involvement, n (%)	4 (1.4)
Neuropsychiatric involvement, n (%)	15 (5.2)
Serositis, n (%)	66 (23.2)
ANA test positivity, n (%)	264 (92.9)
Anti ds-DNA positivity, n (%)	234 (80.9)
ENA profile, ever, n (%)	
Anti-Sm, n (%)	82 (28.8)
Anti-RNP, n (%)	83 (29.2)
Anti-SSA, n (%)	108 (38)
Anti-SSB, n (%)	88 (30.9)
Anti-histon, n (%)	102 (35.9)
Anti-nucleosome, n (%)	97 (34.5)
Lymphopenia, n (%)	110 (38.7)
Low complement levels (C3,C4), n (%)	186 (65.4)
AFAS antibody positivity, n (%)	114 (40.1)
Glucocorticoid use, (ever), n (%)	224 (78.8)
Hydroxychloroquine use, (ever)	258 (90.8)
Immunosuppressive (IS) drug use (ever)	
1 IS	167 (58.8)
2 IS	54 (19)
IS 3 and above	19 (6.6)
ANA: antinuclear antibody, ds-DNA: double-stranded DNA, IS: immunosuppressive, SLE: systemic lupus erythematosus, SD: standard deviation	

Table 2. Distribution of comorbid diseases in SLE patients	
Comorbid diseases	All SLE patients n=284 (%)
Arterial hypertension	68 (23.9)
Diabetes mellitus	16 (5.6)
Dyslipidaemia	30 (10.5)
Coronary artery disease	13 (4.5)
Cardiac arrhythmias	16 (5.6)
Congestive heart failure	6 (2.1)
Chronic kidney disease	23 (8.0)
Cerebrovascular event	12 (4.2)
Osteoporosis	27 (9.5)
Avascular necrosis	11 (3.8)
Chronic obstructive pulmonary diseases	15 (5.2)
Autoimmune thyroid diseases	25 (8.8)
Malignancy	2 (0.7)
SLE: systemic lupus erythematosus	

Table 2 shows the distribution of comorbid diseases in all SLE patients. The most common comorbid disease in patients with SLE was arterial hypertension (23.9%). Other frequently observed comorbidities were dyslipidaemia (10.5%) and osteoporosis (9.5%) respectively.

When stratified by age at diagnosis, 27 patients (7.1%) had childhood-onset SLE, 176 (61.9%) had adult-onset SLE, and 81 (28.5%) had late-onset SLE. Arterial HT was

significantly more frequent in the late-onset SLE group compared to other groups (46.9% vs. 15.9% and 7.4%, respectively; $p_1=0.004$, $p_2=0.0021$). Similarly, osteoporosis was more prevalent (22.2% vs. 4.5% and 3.7%; $p_1=0.014$, $p_2=0.032$). No statistically significant differences was observed among the groups in other comorbidities. Table 3 details the distribution of comorbidities according to SLE groups.

Table 3. Differences of comorbid diseases in childhood SLE, adult onset SLE, late onset SLE				
Comorbid diseases	Childhood-onset SLE <18years n=27 (%)	Adult-onset SLE (18-49 years) n=176 (%)	Late-onset SLE ≥50 years n=81 (%)	p*
Arterial Hypertension	2 (7.4)	28 (15.9)	38 (46.9)	<0.001
Diabetes Mellitus	0	7 (3.9)	9 (11.1)	0.27
Dyslipidaemia	0	11 (6.2)	19 (23.4)	0.063
Chronic kidney disease	2 (7.4)	10 (5.6)	11 (13)	0.73
Coronary Artery Disease	0	6 (3.4)	7 (8.6)	0.87
Congestive heart failure	0	1 (0.5)	5 (6.2)	0.61
Cerebrovascular event	1 (3.7)	3 (1.7)	8(18.5)	0.06
Osteoporosis	1 (3.7)	8 (4.5)	18 (22.2)	0.022
Avascular necrosis	1 (3.7)	6 (3.4)	4 (4.9)	0.42
Chronic obstructive pulmonary diseases	1 (3.7)	10 (5.7)	4 (4.9)	0.60
Autoimmune thyroid diseases	6 (22.2)	11 (6.2)	8 (9.8)	0.06
Malignancy	0	1 (0.5)	1 (1.2)	0.43

SLE: systemic lupus erythematosus; *p1 Comparision between late onset SLE and adult onset SLE, p2 Comparision between late onset SLE and childhood SLE

DISCUSSION

In our study, arterial hypertension emerged as the most common comorbidity among SLE patients (23.9%), with a significantly higher prevalence in the late-onset SLE group. Osteoporosis was also notably more frequent. Contrariwise, autoimmune thyroid diseases were more prevalent in childhood-onset SLE.

Arterial HT is more prevalent among patients with SLE than in the general population, according to previous studies (12,13). Bruce IN. et al. found HT rate of 33% among 250 SLE patients, than controls (13%) ($p=0.001$) (14). Similarly, a large study involving 1042 SLE patients reported a 20.8% HT prevalence (8). The prevalence of HT in late-onset patients was 46.9%, compared to 15.9% in adult-onset patients ($p<0.001$) in our SLE patients. These findings were similar with Riveros Frutos A. et al., who found HT in 51.6% of late-onset versus 25.1% of adult-onset patients (15). Kang JH. et al. also reported higher rates in Korean late-onset SLE patients (24 vs 4%) (16). Studies have emphasized that the frequency of HT is not increased in age- and gender-matched SLE patients. It has been suggested that age may be a contributing factor to the development of high arterial HT in late-onset SLE patients (17).

In our study, osteoporosis was observed in 8.8% of all patients and in 22.2 % of those with late-onset SLE. Yee et al. reported a 10.3% osteoporosis rate among 242 SLE patients (18). In a study using a 45-year cutoff for late-onset, osteoporosis was observed in 11.4% of patients, with significantly higher rates compared to adult-onset patients

(9). Another study comparing 73 late-onset and 144 adult-onset patients found higher osteoporosis prevalence in the late-onset SLE (9.5% vs. 0.6%, $p=0.017$) (19). Our findings support the conclusion that osteoporosis is more frequent.

We found thyroid diseases in 9.1% of all SLE patients, with the highest frequency in childhood-onset SLE (22.2%), compared to 6.2% in adult-onset and 9.8% in late-onset SLE. The small size of the childhood-onset group ($n=27$) might be a contributing factor in our study. A prior study of 524 SLE patients reported thyroid disease in 6.1% (20). While some studies found no significant differences across age groups (21), Tomic-Lucic A. et al. found slightly increased rate of hypothyroidism in early-onset SLE (10% vs. 3.3%) (22).

In our study, DM was observed to be slightly more prevalent in late-onset patients (11.1%) compared to other groups (3.9% and 0%, $p=0.27$). Other studies have reported varying results. It is reported by Ward MM. et al. that 14.7% of DM occurs in cases of late-onset SLE and 4.3% in cases of childhood-onset SLE (23). In contrast, the findings of Bertoli AM. et al. indicated a higher DM prevalence in adult-onset compared to late-onset SLE (10.9% vs. 0.69%, $p=0.01$) (20). Das Chagas Medeiros MM. et al. found a DM prevalence of 13.3% in late-onset and 8.2% in adult-onset patients, though the difference was not statistically significant (21).

Several limitations are presented by this study. Due to its retrospective design, data on potential confounders such as disease activity scores could not be consistently captured. In late-onset patients, cumulative glucocorticoid

exposure may have contributed to osteoporosis and steroid-induced diabetes, but this could not be quantified. Our study highlights into the age-related distribution of comorbidities among SLE patients in a real-world tertiary care setting.

CONCLUSION

Arterial HT and osteoporosis may be present in late-onset SLE compared to those with earlier-onset disease. The presence of comorbid conditions in this subgroup may significantly impact organ damage. Therefore, in addition to disease-specific management, addressing comorbidities should be managed in late-onset SLE to improve clinical outcomes.

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Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: This study received the necessary ethical approval from the Ethics Committee of Gülhane Training and Research Hospital (Date: 06 May 2025; Decision number: 2025/272).

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Diagnostic Performance of Immature Granulocytes in the Early Diagnosis of Acute and Perforated Appendicitis in Children: A Retrospective Study

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Abstract

Aim: Timely identification and intervention in acute appendicitis (AA) are essential to avoid complications. Despite technological advances in diagnostics, challenges persist, particularly in pediatric populations. As a result, the search continues for reliable, rapid, low-cost, and accessible biomarkers. Immature granulocytes (IGs) have recently been proposed as promising indicators of inflammation severity. This study aims to evaluate the diagnostic function of IG and its percentage in distinguishing AA from perforated appendicitis (PA) in pediatric population.

Material and Method: A retrospective study was performed, comprising 201 pediatric cases who had surgery due to appendicitis and 42 healthy controls. Participants were categorized based on histopathological findings into AA, PA, and control groups. Laboratory variables including white blood cell (WBC) count, hemoglobin (Hb), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), platelet count (PLT), IG, %IG, and C-reactive protein (CRP) were compared across groups. Diagnostic performance was assessed through Receiver Operating Characteristic (ROC) curve analysis.

Results: No significant variations were observed in PLT and MPV values. However, significant differences were detected in WBC, CRP, Hb, lymphocyte, monocyte, neutrophil, IG, and %IG levels across the study cohorts ($p < 0.001$ for most; Hb: $p = 0.001$). In PA, IG and %IG showed area under the curve (AUC) values of 0.956 and 0.930. In AA, AUC values were 0.929 for IG and 0.924 for %IG. Cutoff points of 25 (IG) and 0.25 (%IG) yielded good sensitivity and specificity for both conditions.

Conclusion: IG and %IG may provide valuable support in diagnosing AA and PA in pediatric patients. However, their use should complement clinical and laboratory assessments rather than serve as independent diagnostic tools.

Keywords: Acute appendicitis, immature granulocyte, paediatric, perforated appendicitis

INTRODUCTION

In pediatric populations, acute appendicitis (AA) continues to be a predominant clinical indication for emergency abdominal surgery (1). Although medical advances have improved diagnostic strategies, early diagnosis in children remains challenging because of the difficulties in acquiring a dependable patient history, unclear physical assessment findings, and varied presentation of symptoms (2). Despite established diagnostic protocols such as patient history, physical evaluation, laboratory analysis and imaging techniques,

perforated appendicitis is diagnosed in approximately 30% of children under 5 years old. For older children, atypical symptomatology or delayed clinical presentation contribute to diagnostic delays in approximately 28-57% of cases (2).

Although various imaging techniques and clinical evaluation tools are available, limitations such as radiation exposure, operator dependency, cost, and high negative laparotomy rates emphasize the need for more accurate, noninvasive, and accessible diagnostic methods for appendicitis in children (3-6).

CITATION

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Recent research has increasingly focused on identifying biomarkers that can distinguish acute appendicitis from its perforated appendicitis (PA). While traditional markers such as hyperfibrinogenemia and hyponatremia continue to be evaluated, new candidates such as pentraxin-3, ischemia-modified albumin and leucine-rich α -2-glycoprotein 1 have shown potential diagnostic value in identifying perforation (7-12). Similarly, inflammatory mediators such as hyperbilirubinemia and interleukin-6 have been investigated for their prognostic significance (13,14). However, most of these biomarkers face challenges in daily clinical use due to their high cost, invasive sampling requirements or limited methodological accessibility. In this light, parameters derived from the complete blood count (CBC), which are both affordable and widely available, are receiving increasing attention. Indices such as total leukocyte, neutrophil ratios, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) have been evaluated for their potential to predict PA (15-18). Although promising, inconsistent sensitivity and specificity results have limited their clinical use, highlighting the need for simpler, faster and non-invasive diagnostic approaches to minimize unnecessary surgeries and prevent complications.

Immature granulocytes (IGs), refer to early-stage granulocytic cells—such as promyelocytes, myelocytes, and metamyelocytes—that are released from hematopoietic tissues during systemic inflammatory processes. In the context of systemic infection, hematopoietic activation promotes the migration of IGs into the circulating blood, a phenomenon commonly observed as increased IG levels in standard blood panel results (19). Despite their availability in standard blood tests, IG values are frequently overlooked by clinicians, largely due to limited awareness of their diagnostic relevance. Nevertheless, IG measurements meet many of the ideal criteria for a biomarker: they are cost-effective, rapidly obtainable, widely accessible, and reproducible (15,16). Recent research has suggested that both the absolute count and percentage of IGs could act as more robust markers for infection intensity than conventional markers, including white blood cell count (WBC), C-reactive protein (CRP), or the NLR (19-21). However, despite their potential, IG metrics have not yet become a standardized component of infectious disease diagnostics. The objective of this research is to examine the diagnostic advantage of IG count and percentage in identifying early-stage AA, as well as in differentiating its uncomplicated and complicated variants, relative to conventional inflammatory indicators such as WBC, CRP, and NLR.

MATERIAL AND METHOD

This analysis was performed involving 243 individuals, comprising 201 children who received surgical treatment due to AA and 42 healthy children (control group). Two main groups were formed as appendicitis group and the control group. The appendicitis group was categorized into two subgroups, AA and PA, based on histopathologic examination results.

Inclusion Criteria

Patient group:

- Patients children who underwent surgical operation with a prediagnosis of appendicitis.

Control group:

- Children who were admitted for routine health screening or vaccination and did not have any acute infection or inflammatory disease.

Exclusion Criteria

The study excluded patients with indications for surgery other than appendicitis, chronic inflammatory bowel disease, immunosuppressive/steroid therapy, history of active infection, trauma patients, patients with chronic systemic/cardiovascular/ischemic/gastrointestinal diseases, individuals over 18 years of age and those with missing data.

Data Collection and Analysis

Demographic characteristics, clinical findings, laboratory parameters, imaging (abdominal USG/CT) and pathology reports were obtained retrospectively via the electronic patient record system.

Ethical Approval

The study protocol was approved by Hitit University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 31/01/2023 and numbered 2023/09.

Statistical Analysis

The data obtained from measurements in our study were analyzed using the SPSS software (Version 22, SPSS Inc., Chicago, IL, USA). Continuous variables were described using either mean $\pm$ standard deviation or median (min–max), depending on whether the distribution was normal. Categorical variables were expressed as frequencies (n) and percentages (%). The normality of continuous data was assessed via the Kolmogorov-Smirnov test. For comparisons among more than two independent groups, one-way ANOVA was applied when the data followed a normal distribution, while the Kruskal-Wallis test was employed for non-normally distributed data. Following these analyses, post-hoc tests such as Tukey's or Dunn-Bonferroni were conducted to identify specific group differences. Chi-square tests were used to assess relationships between categorical variables, considering cell frequencies during test selection. To evaluate the diagnostic value of laboratory parameters in predicting perforated and acute appendicitis, Receiver Operating Characteristic (ROC) curve analysis was performed. The area under the curve (AUC) with its 95% confidence interval was calculated. AUC values were interpreted as follows: 0.9–1.0: excellent; 0.8–0.9: good; 0.7–0.8: fair; 0.6–0.7: poor; and 0.5–0.6: not useful. The optimal cut-off point was determined using the Youden index, which maximizes sensitivity and specificity. The diagnostic performance of these thresholds was evaluated through

sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 243 patients including 42 (17.3%) control group, 37 (15.2%) PA group, and 164 (67.5%) AA group, were

included. The mean age of the individuals was 12.25±3.15 years, 85 (35%) were female and 158 (65%) were male. Socio-demographic features and laboratory tests of the groups were calculated. (Table 1). No significant variations were observed between PLT and MPV values between the groups (p>0.05). CRP, WBC, Hb, lymphocyte, monocyte, neutrophil, IG (number) and IG (percentage) values were statistically significantly different (p<0.001; Table 1).

Table 1. Comparison of laboratory blood values and clinical and demographic characteristics among research groups					
	Control (n=42) (1)	Perforated appendicitis (n=37) (2)	Acute appendicitis (n=164) (3)	P values	Post-hoc P values
Gender					
Female	20 (47.6%)	13 (35.1%)	52 (31.7%)	0.155 ^a	-
Male	22 (52.4%)	24 (64.9%)	112 (68.3%)		
Age	11.48±2.96	12.42±2.84	12.41±3.95	0.684 ^b	-
CRP	3.3 (3-3.33) (3.229±0.101)	62.4 (3.3-278) (76.56±76.00)	9.96 (3-174) (24.89±33.82)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:<0.001
WBC	8025 (4780-14130) (8254±1745)	14390 (6770-32880) (16092±6295)	13505 (4540-26740) (13982±4886)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.365
HB	12.45 (10-18.4) (12.63±1.595)	13.30 (9.6-15.8) (12.94±1.330)	13.45 (10.3-17) (13.38±1.418)	0.001 ^c	1-2:0.361 1-3:0.001 2-3:0.419
PLT	326000 (139000-543000) (327380±99956)	275000 (165000-484000) (298270±73346)	293000 (74000-502000) (296908±78206)	0.202 ^c	-
MPV	9.75 (8.5-12.6) (9.897±0.845)	9.4 (7.9-11.9) (9.597±0.788)	9.7 (8-12.1) (9.745±0.779)	0.331 ^c	-
Lymphocyte	3820 (990-8940) (3954±1869)	1780 (460-4620) (1742±943.5)	1855 (580-7900) (2011±1060)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.568
Monocytes	520 (350-820) (542.14±111.06)	970 (70-3330) (1065±621.6)	860 (80-3740) (894.7±461.9)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.458
Neutrophil	3435 (930-7560) (3509±1462)	11890 (4830-27790) (12948±5415)	10720 (1720-24960) (11040±4988)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.315
Immature granulocyte (number)	10 (0-20) (11.9±4.547)	50 (10-720) (104.5±148.4)	40 (0-1000) (53.6±81.32)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.149
Immature granulocyte (percent)	0.1 (0-0.2) (0.133±0.052)	0.4 (0.1-4.2) (0.556±0.711)	0.3 (0-3.7) (0.333±0.290)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.177
NLR	0.93 (0.17-5.55) (1.29±1.22)	8.26 (1.18-35.96) (10.24±7.55)	5.29 (0.28-34.19) (7.58±6.08)	<0.001 ^c	1-2:<0.001 1-3:<0.001 2-3:0.100
^a Chi-Square with n (%); ^b One-way ANOVA with mean±standard deviation (SD); ^c Kruskal wallis test with median (min-max); CRP: C-reactive protein, WBC: white blood cell count, HB: hemoglobin, PLT: platelets, MPV: mean platelet volume, NLR: neutrophil-to-lymphocyte ratio					

CRP levels were significantly greater in both AA and PA groups compared to the control group (both p<0.001; Table 1). CRP levels in the PA group were significantly elevated than the AA group (p<0.001; Table 1). Similarly, WBC counts showed significant increases in both AA and PA groups versus controls (both p<0.001; Table 1). Lymphocyte counts were significantly decreased in both appendicitis groups than controls (both p<0.001),

while neutrophil counts were significantly elevated (both p<0.001). Additionally, both absolute IG counts and IG percentages were significantly higher in AA and PA groups than in controls (all p<0.001).

Accuracy values of laboratory parameters in the prediction of AA and PA calculated by ROC analysis using 95% confidence intervals and cut-off values are given in Tables 2 and 3.

Table 2. ROC analysis results, sensitivity, specificity, positive-negative predictive values and accuracy values of laboratory parameters in the prediction of perforated appendicitis

	CRP	WBC	Lymphocyte	Monocytes	Neutrophil	Immature granulocyte (number)	Immature granulocyte (percent)
AUC (95% CI)	0.991 (0.973-1)	0.925 (0.858-0.992)	0.880 (0.803-0.956)	0.837 (0.742-0.932)	0.986 (0.970-1)	0.956 (0.907-1)	0.930 (0.871-0.989)
P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Cut off point for patient	≥4.055	≥11260	≤2410	≥790	≥7005	≥25	≥0.25
Sensitivity	0.972 (0.841-0.998)	0.837 (0.673-0.932)	0.864 (0.704-0.949)	0.648 (0.474-0.792)	0.891 (0.736-0.964)	0.837 (0.673-0.932)	0.756 (0.584-0.876)
Specificity	1 (0.895-1)	0.928 (0.794-0.981)	0.833 (0.680-0.924)	0.976 (0.859-0.998)	0.976 (0.859-0.998)	1 (0.895-1)	1 (0.895-1)
PPV	1 (0.879-1)	0.911 (0.751-0.976)	0.820 (0.658-0.918)	0.960 (0.776-0.997)	0.970 (0.829-0.998)	1 (0.862-1)	1 (0.849-1)
NPV	0.976 (0.862-0.998)	0.866 (0.725-0.944)	0.875 (0.723-0.953)	0.759 (0.620-0.860)	0.911 (0.778-0.971)	0.875 (0.740-0.948)	0.823 (0.686-0.911)
Accuracy	98.7%	88.6%	84.8%	82.2%	93.6%	92.4%	88.6%

ROC: receiver operating characteristic, CRP: C-reactive protein, WBC: white blood cell count, AUC: area under curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

Table 3. ROC analysis results, sensitivity, specificity, positive-negative predictive values and accuracy values of laboratory parameters in the prediction of acute appendicitis

	CRP	WBC	HB	Lymphocyte	Monocytes	Neutrophil	Immature granulocyte (number)	Immature granulocyte (percent)
AUC (95% CI)	0.800 (0.742-0.858)	0.871 (0.821-0.921)	0.675 (0.584-0.766)	0.835 (0.763-0.907)	0.790 (0.731-0.849)	0.939 (0.907-0.970)	0.929 (0.895-0.963)	0.924 (0.887-0.960)
P values	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Cut off point for patient	≥3.335	≥10505	≥13.15	≤2265	≥715	≥4385	≥25	≥0.25
Sensitivity	0.682 (0.605-0.752)	0.750 (0.675-0.812)	0.585 (0.505-0.660)	0.670 (0.592-0.740)	0.640 (0.561-0.712)	0.926 (0.872-0.959)	0.774 (0.701-0.834)	0.701 (0.624-0.768)
Specificity	1 (0.895-1)	0.904 (0.764-0.969)	0.738 (0.576-0.856)	0.880 (0.735-0.955)	0.952 (0.825-0.991)	0.857 (0.707-0.940)	1 (0.895-1)	1 (0.895-1)
PPV	1 (0.958-1)	0.968 (0.916-0.989)	0.897 (0.819-0.945)	0.956 (0.896-0.983)	0.981 (0.927-0.996)	0.962 (0.915-0.984)	1 (0.963-1)	1 (0.959-0.999)
NPV	0.446 (0.345-0.552)	0.481 (0.368-0.595)	0.313 (0.225-0.415)	0.406 (0.306-0.514)	0.404 (0.308-0.507)	0.750 (0.601-0.858)	0.531 (0.416-0.643)	0.461 (0.357-0.568)
Accuracy	74.7%	78.1%	61.6%	71.3%	70.3%	91.2%	82%	76.2%

ROC: receiver operating characteristic, CRP: C-reactive protein, WBC: white blood cell count, HB: hemoglobin, AUC: area under curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

As a result of ROC analysis, Hb, PLT, MPV parameters were not statistically significant in predicting PA: 0.618 (0.493-0.744), p=0.071; 0.593 (0.466-0.719), p=0.157; 0.598 (0.472-0.724), p=0.135, respectively).

ROC analysis showed that CRP, WBC, lymphocyte, neutrophil, IG and immature granulocyte (percent) parameters were significant in predicting PA (AUC=0.991 (0.973-1); AUC=0.925 (0.858-0.992), AUC=0.880 (0.803-0.956), AUC=0.986 (0.970-1), AUC=0.956 (0.907-1), AUC=0.930 (0.871-0.989), Table 2). ROC curves for perforated appendicitis control differentiation are shown in Figure 1.

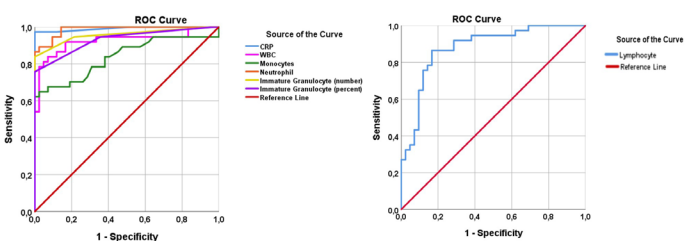


Figure 1. a. The area under the ROC curve for perforated appendicitis-control discrimination by CRP, WBC, Monocytes, Neutrophil, Immature Granulocyte (percent) and Immature Granulocyte (number) values; b. The area under the ROC curve for perforated appendicitis control discrimination by Lymphocyte values

The cut-off value for CRP value was 4.055; sensitivity was 97.2% and selectivity was 100%. The cut-off value for WBC value was 11260; sensitivity was 83.7% and selectivity was 92.8% (Table 2). The cut-off value for neutrophil value was 7005; sensitivity was 89.1% and selectivity was 97.6%. The cut-off value for IG value was 25; sensitivity was 83.7% and selectivity was 100%. The cut-off value for %IG value was 0.25; sensitivity was 75.6% and selectivity was 100% (Table 2).

PLT and MPV parameters were not significant in predicting acute appendicitis (AUC:0.586 (0.485-0.688), $p=0.084$; AUC: 0.534 (0.438-0.629), $p=0.501$, respectively).

As a result of ROC analysis, CRP, WBC, HB lymphocytes, monocytes, neutrophils, IGs (number) and IGs (percentage) parameters were detected to be significant in predicting AA (AUC=0.800 (0.742-0.858); AUC=0.871 (0.821-0.921), AUC=0.675 (0.584-0.766), AUC=0.835 (0.763-0.907), AUC=0.790 (0.731-0.849), AUC=0.939 (0.907-0.970), AUC=0.929 (0.895-0.963), AUC=0.924 (0.887-0.960), Table 3). ROC curves for acute appendicitis control differentiation are shown in Figure 2.

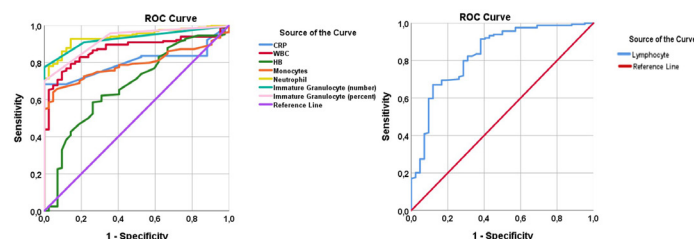


Figure 2. a. The area under the ROC curve for acute appendicitis-control discrimination by CRP, WBC, HB, Monocytes, Neutrophil, Immature Granulocyte (percent) and Immature Granulocyte (number) values; **b.** The area under the ROC curve for acute appendicitis –control discrimination by Lymphocyte values

The cut-off point for CRP value was found to be 3.335. The classification success for this cut-off point was found to be 68.2% with a sensitivity of 68.2% and a selectivity of 100%. The cut-off point for WBC value was 10505; sensitivity was 75% and selectivity was 90.4%. The cut-off value for lymphocyte value was 2265; sensitivity was 67% and selectivity was 88%. The cut-off value for neutrophil value was 4385; sensitivity was 92.6% and selectivity was 85.7%.

The cut-off value determined IG value was 25; sensitivity was 77.4% and selectivity was 100%. The cut-off point for %IG was 0.25; sensitivity was 70.1% and selectivity was 100% (Table 3).

DISCUSSION

Although appendicitis represents a frequently encountered abdominal emergency in the pediatric population, its diagnosis typically relies on clinical assessment, laboratory findings, and imaging techniques. However, in the absence of definitive clinical signs and when these conventional methods yield inconclusive results, additional diagnostic support may be required. The use of reliable biomarkers in addition to clinical

findings may facilitate accurate diagnosis and reduce negative appendectomy rates. WBC, ANC, NLR, platelet distribution width (PDW) and CRP are among the most commonly examined parameters in the diagnosis of AA and widely used in clinical practice (18-20,22).

Especially WBC is accepted as a basic marker that increases in the early period in AA and reflects the inflammatory response. Studies have reported a significant predictive value of WBC in pediatric population with complicated appendicitis (23). However, it has been shown that the values of WBC and CRP are not sufficient to exclude AA (24), and the observation of a wide variability in WBC values between complicated and uncomplicated appendicitis groups limits the diagnostic value of this parameter (25,26). A recent study reported that patients without acute appendicitis exhibited significantly elevated levels of WBC count, neutrophil count and percentage, monocyte count, NLR, and PLR whereas lymphocyte count and percentage, monocyte percentage, and MLR were significantly lower (27). In alignment with previous findings, our analysis demonstrated that the appendicitis group had notably higher WBC, neutrophil, and monocyte counts, along with significantly lower lymphocyte counts when compared to the control group ($p<0.001$). This neutrophilia and lymphopenia observed led to the use of NLR ratio as an inflammation parameter and studies have suggested that it may be useful in the differentiation of PA (28). In Doğan et al. study, although NLR value was higher than the control group ($p<0.001$), no difference was found between the complicated and AA groups (29). In another study by Anastasakis et al. it was emphasised that NLR facilitated the differentiation between acute and complicated forms of appendicitis (30). In our study, although NLR was identified to be greater in the appendicitis group compared to controls ($p<0.001$), it was not sufficient to differentiate the AA and PA groups. The present data suggest that further studies evaluating standardized and innovative diagnostic tools are needed due to inconsistencies in the clinical performance of biomarkers used in the diagnosis of AA.

Markers related with platelets such as platelet and MPV have also been used to evaluate inflammation and it was found that MPV was affected by inflammation and increased in sepsis and inflammatory diseases (19). However, it has been reported previously that there is no significant variation in MPV between AA and controls or between AA and non-AA cases, and that MPV levels should not determine treatment options in pediatric AA, even though MPV levels seem to be somewhat useful in the diagnosis of adult AA (31). Our findings support the literature.

CRP is an acute phase reactant which is directly associated with the severity of inflammation and it increases in cases of AA and reaches even higher levels in patients with PA. However, some studies have suggested no significant variation between AA and the healthy individuals (22). In a recent study, it was reported that no CRP cut-off point had sufficient sensitivity or specificity to definitively exclude

appendicitis and appendicitis could be missed in 13% of cases even at ≥ 10 mg/L (32). In our study, in contrast to these findings in the literature, CRP levels were determined to be significantly greater in both AA and PA groups compared to the control group, and it was also identified to be statistically significantly higher in the PA group compared to AA. These findings suggest that CRP may be an important marker in the diagnosis of appendicitis and increases in relation to the severity of the disease. However, since there are conflicting results in the literature regarding the diagnostic value of CRP, it is not sufficient alone in the clinical decision-making process and should be evaluated together with other parameters.

IG are premature granulocytes (promyelocytes, myelocytes, metamyelocytes) released from the bone marrow in the presence of infection, inflammation, sepsis and other stimuli (29). In the literature, IG percentage has been shown to have diagnostic and prognostic value in various infectious and inflammatory diseases. In the diagnosis of pediatric acute pyelonephritis, IG percentage has been suggested to be one of the markers with the highest predictive value after CRP (33). In acute necrotizing pancreatitis, IG percentage and immature granulocyte concentration (IGC) were defined to have greater predictive value compared to WBC, NLR and CRP (34). Furthermore, in severe bacterial infections, IG percentage was found to provide additional diagnostic contribution to WBC, ANC, and CRP for predicting the severity of infection (35).

Doğan et al. stated that IG levels were greater in the AA group compared to the healthy control group, but this difference was not significant ($p=0.28$). However, a %IG value $>0.2\%$ in routine complete blood count in patients with suspected AA may be an early and important indicator of PA and has been evaluated as a reliable marker for appendiceal perforation (sensitivity 81.8%, specificity 85.2%, AUC: 0.83) (29). Ünal et al. emphasized that %IG could both distinguish the AA group from the control group and discriminate between the AA and PA group, and that %IG had a higher diagnostic value in predicting PA compared to other parameters (AUC ROC: 0.979, sensitivity 94.4%, specificity 97.9%) (20). In research performed by Güngör et al., the highest area under the ROC values for predicting PA were found to be associated with the percentage of immature granulocytes (IG) [odds ratio (OR): 9.36, 95% CI: 4.94–17.75, $p<0.001$] and CRP levels (36). Similarly, a study by Kubat et al. involving adult patients demonstrated that markers such as the immature granulocyte-to-lymphocyte ratio, NLR, and monocyte-to-lymphocyte ratio could serve as useful parameters in distinguishing AA from PA (37). Another investigation assessed the predictive value of IG count and percentage in diagnosing suspected AA based on the Alvarado value and their influence on the necessity of computed tomography (CT) imaging. The findings indicated that IG count could be a significant predictor of AA in individuals categorized as intermediate risk according to the Alvarado scoring system and may help guide selective CT use (38).

However, there are also studies in the literature whose results are inconsistent with these studies. Mathews et al. found that %IG could differentiate perforated appendicitis in pediatric patients, but when combined with classical inflammatory markers such as white blood cell count, left shift in neutrophils, and CRP, it did not provide an additional diagnostic contribution in the detection of perforated appendicitis (39). Similarly, in the study of Cesur et al., including 108 patients (AA: 48 patients, PA: 9 patients, control: 53 patients), no significant variations were identified between AA and control group and the AA and PA group in terms of IG count and %IG. These results suggest that IG count and %IG may not be a determinant biomarker alone in the differentiation between AA and PA (40).

In our study, IG count and %IG values were significantly greater in the AA and PA, and ROC analyses revealed that IG had a high diagnostic value both diagnosis of AA (AUC: 0.929) and the prediction of PA (AUC: 0.956). Especially in the PA group, IG $\geq 25/\mu\text{L}$ and %IG ≥ 0.25 cut-off values indicated the risk of complications with 100% specificity, suggesting that these parameters may support clinical decision support in case of suspected perforation. While these findings emphasize the diagnostic value of IG and %IG in pediatric patients, they are consistent with some studies in the literature and contradict others. Although there are extensive studies on the differentiation of AA and PA in adult patients, studies examining the diagnostic value of IG and %IG in pediatric patients are limited. Although our findings show that IG is significantly elevated in association with perforation, it should be considered that this increase may be related not only to perforation of the appendix but also to the severity of inflammation and systemic response.

The main features expected from biomarkers are that they should be fast and easy to apply, cost-effective and provide reliable measurements. Today, thanks to modern analyzers, IG and %IG values can be measured within minutes, do not require additional blood samples and do not create additional costs. With these features, IG stands out as a practical and advantageous biomarker that can help in the early diagnosis of AA and PA.

One of the key limitations of this research is its retrospective nature and the fact that it was conducted in a single center, which may restrict the generalizability of the findings. Additionally, the restriction of the patient cohort to a specific geographic area may hinder the extrapolation of these findings to diverse populations or larger clinical settings. To more accurately define the diagnostic utility of IG in acute appendicitis and their potential in predicting perforation, future investigations should be performed on prospective studies that include a wide range of age groups. In addition, standardization of the diagnostic threshold values of IG should be addressed in further studies, considering that hematologic parameters may show age-related variability.

CONCLUSION

Our study shows that IG and %IG have potential value as an adjunctive biomarker in the diagnosis of pediatric AA and PA. However, these parameters should be evaluated together with clinical findings and other laboratory indicators rather than being diagnostic alone. Considering the heterogeneity of the inflammatory response in children and the age-related variability of hematologic parameters, more comprehensive, multicenter, and prospective validation studies are required to improve the diagnostic reliability of IG.

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Ethical approval: The study protocol was approved by Hitit University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 31/01/2023 and numbered 2023/09.

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Parental Knowledge and Management Approaches Toward Pediatric Fever: A Cross-Sectional Survey Study

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Abstract

Aim: This descriptive cross-sectional study aimed to evaluate parental knowledge, attitudes, and practices concerning fever management in children aged 6 months to 6 years.

Material and Method: A structured face-to-face survey was administered to 125 parents at the pediatric infectious diseases outpatient clinic of a tertiary university hospital in İstanbul, Türkiye.

Results: The results revealed that while the majority of parents identified $\geq 38^{\circ}\text{C}$ as the threshold for fever, a notable proportion (27%) reported administering antipyretics below this level, primarily due to fear of febrile seizures (69%). Furthermore, 81% of parents gave antipyretics before consulting a physician, and more than half alternated medications without medical advice. Although modern thermometer use (e.g., non-contact infrared) was widespread, outdated practices such as tactile temperature assessment persisted among a minority. The data indicate a clear association between lower educational attainment and inappropriate fever management behaviors.

Conclusion: These findings underscore the need for targeted educational interventions to address common misconceptions, reduce fever-related anxiety, and promote evidence-based home management strategies. Improving parental knowledge through accessible, culturally appropriate resources could ultimately enhance child health outcomes and alleviate unnecessary strain on pediatric healthcare services.

Keywords: Fever in children, antipyretic use, parental knowledge

INTRODUCTION

Fever is one of the most common symptoms in pediatric practice and a frequent cause of visits to outpatient clinics and emergency departments. Although fever itself is not a disease but rather a physiological response to infection and inflammation, it often generates considerable anxiety among parents. This phenomenon, commonly referred to as "fever phobia," leads caregivers to adopt overly aggressive or inappropriate fever management practices, such as the early or unnecessary use of antipyretic medications and frequent healthcare visits (1,2).

Pediatricians are well aware that fever is a natural defense mechanism that can aid in fighting infections. Nevertheless, studies from different regions have consistently demonstrated that many parents perceive fever as a dangerous condition and associate it with severe

complications such as febrile seizures, brain damage, or even death. These misconceptions, combined with insufficient knowledge about accurate fever measurement and management, may result in irrational behavior during febrile episodes, ultimately affecting the quality of care and increasing the burden on healthcare systems (2).

Previous studies conducted in various countries, including Türkiye, have revealed a lack of parental knowledge regarding the definition of fever, appropriate use of thermometers, and safe practices for lowering body temperature. Many parents begin antipyretic treatment at low-grade fever and use alternating medications without medical guidance (3-5).

This study aims to assess the knowledge and attitudes of parents regarding fever in children aged 6 months to 6 years who presented to the pediatric infectious

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diseases outpatient clinic of a tertiary hospital. By identifying gaps in parental understanding and common misconceptions, we aim to highlight the need for targeted educational interventions to promote evidence-based fever management at home.

MATERIAL AND METHOD

This descriptive cross-sectional study was conducted at the pediatric infectious diseases outpatient clinic of a tertiary university hospital in İstanbul, Türkiye. The study included parents of children aged between 6 months and 6 years who presented to the clinic for any reason between January 1 and March 31, 2025. A total of 125 parents who agreed to participate voluntarily and met the inclusion criteria were randomly selected to participate in the study.

Data were collected using a structured questionnaire developed by the researchers based on existing literature. The questionnaire consisted of items assessing sociodemographic characteristics, knowledge about fever, fever measurement practices, approaches to fever management, and commonly used antipyretic methods. The instrument was administered through face-to-face interviews conducted by trained healthcare staff. Each interview lasted approximately 10–15 minutes.

Inclusion and Exclusion Criteria: Parents who had children aged 6 months to 6 years and agreed to participate were included. Those who were healthcare professionals or had a child with a chronic or complex medical condition that could influence fever perception or management were excluded.

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by Ataşehir Memorial Hospital Ethics Committee (date: June 16, 2025 number: 06.2025). Data were analyzed using descriptive statistics. Frequencies and percentages were used to summarize categorical variables.

RESULTS

A total of 125 parents participated in the study between January 1 and March 31, 2025. All participants had at least one child aged between 6 months and 6 years. The majority of respondents were mothers. Regarding the educational background of the participants, 61.6% (n=77) were university graduates, 29.6% (n=37) had completed high school, and 8.8% (n=11) had a primary or middle school education. This distribution reflects a relatively well-educated sample group (Table 1).

When parents were asked about their primary temperature measurement method, most parents (63%) reported using a non-contact infrared thermometer to measure their child’s temperature. Tympanic thermometers were used by 20.8% of parents, while 9.6% measured fever via the axillary route. A small subset (6.4%) stated that they relied solely on tactile assessment, such as touching the child’s forehead, to detect fever. When asked about their understanding of what constitutes a fever, 68% of the parents identified 38°C or higher as the threshold. Interestingly, 27.2% reported

administering antipyretic medications at temperatures below 38°C, reflecting a lowered fever threshold in practice. Nearly all participants expressed considerable concern when their child’s temperature exceeded 39°C. A significant proportion, 68.8%, indicated febrile seizures as their greatest fear during febrile episodes (Table 1).

Most parents (80.8%) reported giving antipyretic medication before consulting a physician. Moreover, 55.2% stated that they alternated between different antipyretics, often without professional guidance. This pattern suggests a tendency toward over-treatment and anxiety-driven management of fever. In addition to pharmacologic intervention, 64% of participants reported attempting to reduce the room temperature as a non-pharmacologic approach to fever. Furthermore, 35.2% stated that they removed the child’s clothing and applied cool compresses as an initial response to elevated body temperature (Table 1).

Table 1. Parental education, fever measurement, and management practices (n= 125)			
Category	Response	n	%
Educational level	University degree	77	61.6
	High school	37	29.6
	Primary/middle school	11	8.8
Fever measurement	Non-contact thermometer	79	63.2
	Tympanic thermometer	26	20.8
	Axillary thermometer	12	9.6
	By touching	8	6.4
Definition of fever	≥38°C considered fever	85	68
	Used antipyretics <38°C	34	27.2
Antipyretic use	Before seeing doctor	101	80.8
	Alternating medications	69	55.2
Non-drug measures	Reduced room temperature	80	64
	Cool compresses	44	35.2
Concerns	Fear of febrile seizures	86	68.8

DISCUSSION

This study provides valuable insights into parental perceptions and management strategies related to fever in children aged 6 months to 6 years. Our findings reveal that although fever is a common and typically benign symptom in childhood, a significant proportion of parents continue to exhibit anxiety-driven practices, including the early use of antipyretics, even at low-grade fever.

One of the most striking findings of our study is the inverse relationship between parental education level and the likelihood of using antipyretics below 38°C. This trend is consistent with previous research conducted in both Türkiye and internationally, which has shown that lower education levels (primary and/or middle school) are associated with increased “fever phobia” and misconceptions about the harmful effects of fever (1,3). In our study, parents with primary or middle school education were nearly 2.5 times more likely to use antipyretics below 38°C compared to university graduates. This suggests that higher education

may confer greater access to accurate health information and better understanding of fever as a physiological defense mechanism. The higher rates of inappropriate antipyretic use among less-educated parents may be due to difficulty accessing accurate health information and a lack of health literacy.

Similar to the findings of Gürarslan Baş et al. (2016) and Nerkiz et al. (2012), most parents in our sample identified fever as a source of serious concern (3,4). Nearly all participants expressed distress when the child's temperature exceeded 39°C, and 69% specifically feared febrile seizures. Although febrile seizures are relatively benign and self-limiting, this fear often drives unnecessary or premature use of antipyretics and leads to frequent hospital visits (5). Studies have shown that such anxiety may lead caregivers to monitor temperature excessively and alternate antipyretics without medical advice. The high rate of antipyretic administration before consulting a physician (80.8%) and the frequent use of multiple antipyretic agents alternately (55.2%) further demonstrate the extent of over-medicalization in fever management (3-6). Given that 55.2% of parent's alternate antipyretics without guidance, pediatricians should provide accurate information about this practice during routine visits. While non-pharmacologic methods such as reducing room temperature and applying cool compresses were also reported, these were secondary to medication use. Similar patterns have been observed in other Turkish studies, indicating that this issue is widespread and systemic (7).

Notably, our study also revealed the widespread use of non-contact infrared thermometers, which may reflect increasing public access to modern tools. However, the minority (6.4%) who relied solely on tactile assessment signals the persistence of outdated practices, particularly among those with lower education levels. Overall, these results underscore the need for targeted parental education focusing on the nature of fever, its benefits, and evidence-based management strategies. Educating caregivers, especially those with lower educational attainment, could reduce unnecessary antipyretic use, minimize healthcare system burden, and foster more confident home care (8).

This study has several limitations that should be considered when interpreting the findings.

First, it was conducted in a single tertiary-care university hospital in Istanbul over a three-month period, which may limit the generalizability of the results to other geographic regions or healthcare settings. Second, the sample size was modest (n=125) and skewed toward parents with higher educational attainment; therefore, prevalence estimates of misconceptions may be lower than in the general population. Third, all information was self-reported and thus subject to recall and social-desirability biases; actual home practices might differ from the behaviors described during the face-to-face interviews. Fourth, the cross-sectional design precludes causal inference, and we did not verify clinical outcomes such as the appropriateness

of antipyretic dosing or the incidence of febrile seizures. Finally, fathers were under-represented, so the results largely reflect maternal perspectives.

CONCLUSION

The study highlights significant gaps in parental knowledge and practices regarding fever management in children. While fever is a common and self-limiting physiological response, many parents perceive it as a dangerous condition requiring immediate pharmacologic intervention. High rates of antipyretic use at low-grade fever and the widespread fear of febrile seizures indicate persistent misconceptions and anxiety-driven responses. Developing educational strategies in primary care and pediatric outpatient clinics to improve parental knowledge will help families acquire accurate practical skills about fever. The clear association between lower educational attainment and inappropriate fever management behaviors underscores the urgent need for targeted educational initiatives. By empowering parents with evidence-based knowledge and practical strategies, healthcare providers can help reduce fever phobia, improve home-based care, and lessen the burden on emergency services.

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Limitations of Diagnostic Ultrasound Use in Rheumatoid Arthritis Rehabilitation: Technical Report

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Abstract

Aim: The purpose of this technical note is to critically evaluate the role of ultrasound in the diagnosis and management of rheumatoid arthritis (RA).

Material and Method: In this study joint distance, effusion area and degree of inflammation were assessed using the GE Color Doppler device. Participants diagnosed with RA are positioned comfortably and the area under examination is completely relaxed.

Results: The primary constraint on the utilisation of ultrasound imaging in the management of RA pertains to the necessity for expertise and experience on the part of the ultrasonographer. In addition, the imaging capacity to visualise deep structures is inadequate, a problem that is exacerbated in obese patients due to inadequate penetration. Thirdly, ultrasound (US) exhibits lower resolution compared to alternative imaging modalities such as Magnetic Resonance Imaging (MRI), resulting in its inability to distinguish subtle bone changes. The fourth limitation relates to the difficulties associated with imaging small joints, such as the hands, due to their size and anatomical complexity. Finally, the effectiveness of ultrasound in identifying synovial thickening and erosions is well documented; however, its inability to differentiate between active inflammation and chronic fibrotic changes may hinder treatment decisions in some cases.

Conclusion: US is a valuable tool in managing RA, but its effectiveness is limited by operator dependency, imaging challenges, and difficulty distinguishing active inflammation from chronic changes. Enhancing training, standardizing protocols, and integrating advanced technologies like artificial intelligence (AI) and hybrid imaging can improve its diagnostic precision and utility in rheumatological care.

Keywords: Diagnostic ultrasound, rheumatoid arthritis, hand rehabilitation, imaging

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disorder, primarily involving the synovial joints, and causing inflammation, pain and progressive joint damage (1). In the absence of adequate treatment or management, RA has the potential to result in severe disability, diminished quality of life, and an elevated risk of morbidity (2). A correct diagnosis is vital for effective treatment, preventing complications, and ensuring continuous monitoring of disease activity (3). This has prompted the exploration of advanced imaging techniques as complements to clinical evaluations and traditional radiography in the management of RA.

Ultrasound (US) imaging has become a cornerstone in the assessment of RA due to its ability to provide detailed,

real-time visualization of soft tissues, synovial structures, and inflammatory processes (4). Unlike conventional radiographs, which are limited to detecting bone damage, US can identify subclinical synovitis, joint effusions, and early erosive changes (5). Moreover, the integration of Doppler technology allows for the evaluation of vascularity within inflamed synovial tissue, offering a reliable surrogate marker for disease activity and response to treatment. These features make US particularly valuable in the early stages of RA, where prompt intervention can prevent irreversible joint damage (6).

Despite its numerous advantages, the use of US in RA is not without challenges. The technique is operator-dependent, requiring a high level of expertise and standardized protocols to ensure reproducibility and accuracy (7).

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Additionally, its limited ability to assess deeper structures and its lower sensitivity in detecting bone erosions compared to advanced modalities like magnetic resonance imaging (MRI) raise concerns about its standalone use in comprehensive disease evaluation (8).

This technical report is based on the problems encountered during the execution of the PhD thesis entitled “Comparison of The Effects of Exercise and Preventive Approach and Mobility Applications on Work, Daily Life Activity and Quality of Life in Patients With Rheumatoid Arthritis”. This technical report aims to critically evaluate the role of US in the diagnosis and treatment of RA, focusing on its advantages and limitations. By examining the usefulness of US in early diagnosis, disease monitoring and treatment guidance, as well as its challenges in clinical practice, this report will provide a perspective on the problems that physiotherapists may encounter in the use of US in rheumatological rehabilitation.

Technical Report

This study was conducted between October 2023 and December 2024 at Kırşehir Ahi Evran University School of Physical Therapy and Rehabilitation. Ethical approval of the study was obtained from Haliç University Non-Interventional Studies Ethics Committee with the number 2023/64. Voluntary consent form was signed by the participants. Joint distance, effusion area and degree of inflammation were assessed using the GE Versana US device. Doppler adjustments were made as shown in the table below. The assessment results were recorded in the US results report (Table 1). The patient is positioned comfortably and the area under examination is completely relaxed, as tension in the muscles and tendons will cause a slight tremor, which can lead to movement disorders. Patient position and probe placement were determined as previously described in the literature (9).

Table 1. Device settings	
Setting	Value
Pulse repetition frequency	0.5*
Color priority	All priorities are given to color.
Wall filter	40-53*
Persistence	18*
Gain	Noise threshold-0.5
Focus	Placed where the highest precision is required
*Set as low as possible	

A significant limitation of US imaging in the management of RA is its considerable reliance on the expertise. Variations in image acquisition and interpretation can result in misjudgement of synovitis and erosions, underscoring the necessity for standardised training programmes and certification processes to ensure accurate assessments. Integration of physiotherapists into diagnostic processes can help reduce operator-related variability. The integration of artificial intelligence (AI)-assisted tools may help to improve the skills of physiotherapists, especially those with limited experience in image interpretation.

An important difficulty encountered during the study was that the first US images obtained were distorted because the ultrasonographer with limited experience was assigned to various hospitals during rotation assignments (Figure 1). While measures have been implemented to mitigate data loss, the involvement of an experienced US assessor, under the supervision of a designated individual, is recommended in subsequent studies to enhance the reliability of the results (Figure 2).

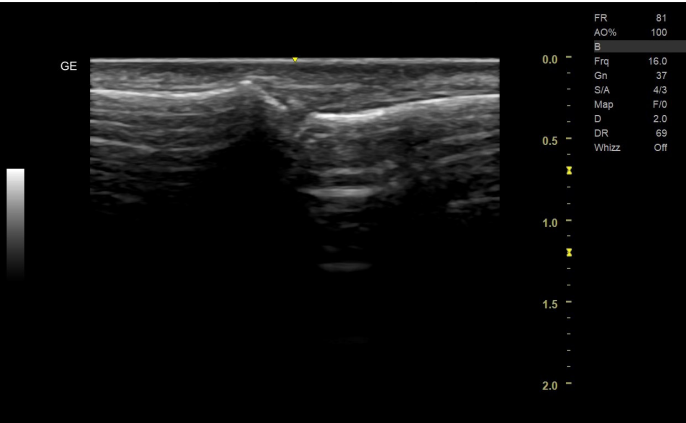


Figure 1. Distorted ultrasound image

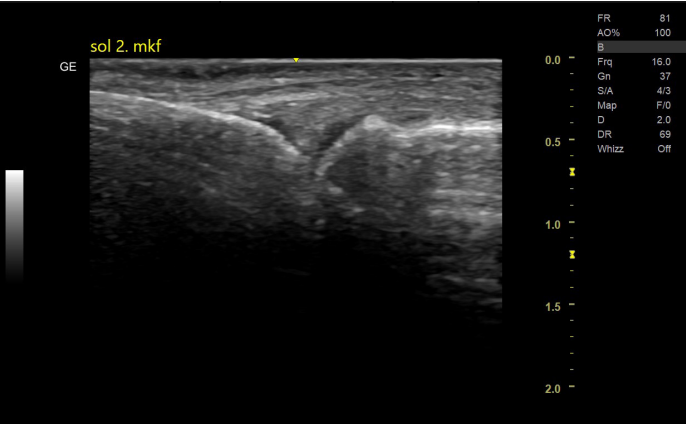


Figure 2. Image captured by an expert

A secondary limitation inherent in US is its inadequate capacity to visualise deep structures; this problem is exacerbated in obese patients due to insufficient penetration. The data from obese patients in our study revealed a significant difficulty in visualising the wrist joint in particular (Figure 3).

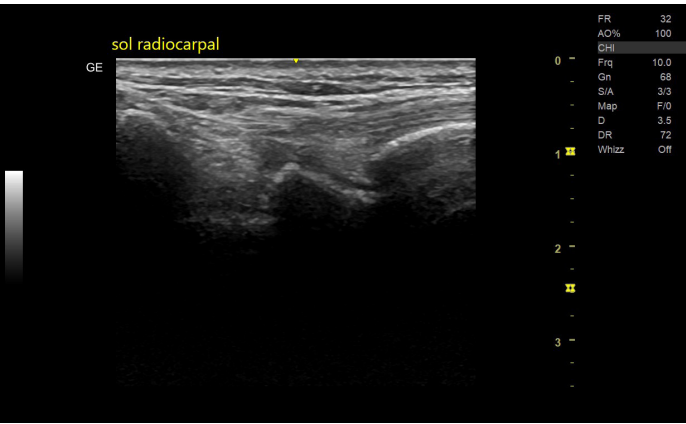


Figure 3. The image of obese patients

Moreover, US exhibits inferior resolution when compared to alternative imaging modalities, such as MRI, resulting in its inability to discern subtle bone changes. In the present study, no parameters related to bony structures were examined; therefore, no limitations were encountered in this regard. However, improvements in transducer technology and software may enhance resolution and penetration, leading to superior visualisation of deep structures and small joints.

The third limitation pertains to the challenges associated with imaging small joints, such as the hands, due to their size and anatomical complexity. This can result in an underestimation or complete oversight of the degree of inflammation in these areas. Despite the existence of various scoring systems for US assessment in RA, such as the OMERACT US definitions, a universal standard remains elusive. This has given rise to inconsistencies in the assessment of disease activity across different healthcare providers. The potential exists for the development of a universally accepted scoring system through international cooperation between rheumatology and radiology associations. A semi-quantitative scoring system was employed in our study to assess the degree of inflammation as much as possible, in recognition of these problems (10).

Finally, the effectiveness of US in identifying synovial thickening and erosions is well documented; however, its inability to distinguish between active inflammation and chronic fibrotic changes may, in some cases, impede treatment decisions. The use of US in combination with other imaging modalities such as MRI or computed tomography (CT) will provide a more comprehensive evaluation. The present study included established RA patients with a DAS-28 score of less than 5.1, and durations are more than 3 years, thus focusing on joints with fibrotic changes rather than active inflammation in this condition. Although Doppler technology is a more effective method for monitoring active inflammation in color, it was used for grading inflammation in the present study.

DISCUSSION

Ultrasonography is a reliable tool for estimating the size of the joint space and assessing synovial activity through vascularization and flow patterns. It is especially useful for monitoring synovial inflammation in RA (9). Correct interpretation of Doppler flow images requires knowledge of technical factors affecting the Doppler signal (11). Artefacts, which may result from physical limitations of the modality or inappropriate equipment settings, can significantly distort the imaging of flow conditions (12). In our study, some of the artefacts in the use of US were caused by the sonographer, especially in the initial assessments. Replacing the sonographer with an experienced sonographer prevented human error. Additionally, a negative Doppler signal does not exclude synovitis, while a positive signal indicates active synovial inflammation but does not correlate with the extent of the inflammation (13). Consequently, it is imperative to

undertake regular checks of the calibration of US devices to ensure the reliability of evaluations. The equipment we used was received new and fully calibrated. Therefore, we did not lose any data due to a calibration error caused by the device.

A 2018 study compared conventional Power Doppler Ultrasound (PDUS) with three-dimensional PDUS and noted that although PDUS offers superior sensitivity for detecting synovial vascularity, challenges remain in standardising and quantifying its results (14). Another study proposes the integration of automated algorithms with the objective of reducing variability in flow pattern interpretation and identifying artefacts. For instance, the utilisation of AI for image analysis has been proposed as a means of enhancing the accuracy of Doppler signal detection and reducing operator dependency (15). Moreover, hybrid imaging combining US and MRI has shown promise in providing a comprehensive view of joint pathology by overcoming US's depth limitations (16). US enables the detection and grading of destructive and inflammatory changes in the MTP joints of patients with RA (17). Compared with MRI, US has been found to be significantly more sensitive and accurate than clinical examination and conventional radiography. Given the early and frequent involvement of metacarpophalangeal joints, evaluation of these joints with US may be of great clinical importance in RA (18). In addition, imaging plays an important role in the diagnosis of PsA which is another rheumatological problem. Classical radiography allows the identification of late stages of the disease when bone tissue is affected (19). However, US, CT and MRI have been developed and have become important diagnostic tools in the evaluation of rheumatoid diseases. They allow the evaluation and monitoring of early inflammatory changes (20). While conventional radiographs show only late signs of past disease activity, there is evidence that MRI and US are highly sensitive for early inflammatory and destructive changes in RA joints, and that MRI findings are sensitive to change and have predictive value for future progressive radiographic damage. On this basis, the use of MRI and US for the detection of arthritic joint pathology and MRI for the monitoring and prognosis of early RA can be recommended (21).

In order to advance the field, it is essential to conduct additional studies with a focus on the development of methodologies for the prevention of artifacts and the establishment of standards for the calibration of devices. It is vital that physiotherapists and clinicians adhere to the guidelines set out for musculoskeletal US (10,22,23), integrating these principles into rheumatological rehabilitation assessments. In order to enhance the accuracy of diagnoses, collaborative efforts between rheumatologists, physiotherapists, and radiologists are required.

CONCLUSION

This study highlights several limitations that impact its effectiveness, including operator dependency, challenges in

imaging deep and small joints, and difficulty distinguishing between active inflammation and chronic fibrotic changes. The findings underscore the importance of standardized training programs, device calibration, and the development of universal scoring systems to enhance the reproducibility and accuracy of US evaluations in RA.

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