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## CONTENTS

### Original Articles

İstanbul Med J 2026; 27(1): 1-6
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# Evaluation of Postoperative Cognitive Function in Patients Undergoing General or Spinal Anesthesia During Extremity Surgery: A Prospective Cohort Study

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## ABSTRACT

**Introduction:** This research investigates the impact of general anesthesia (GA) and spinal anesthesia (SA) on cognitive function following extremity surgery.

**Methods:** A prospective cohort study was conducted with 60 patients (30 GA, 30 SA) undergoing elective extremity surgery. Cognitive function was assessed preoperatively and at 4 and 24 hours postoperatively using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).

**Results:** At 4 hours postoperatively, MoCA scores were significantly higher in the SA group (21.6±2.6) compared to the GA group (20.8±4.4; p<0.001). By 24 hours, cognitive recovery was more pronounced in the SA group (22.7±2.8) than in the GA group (22.0±4.2) (p=0.001). MMSE scores followed a similar trend: at 24 hours, SA patients had a significantly higher score (26.1±2.3) than GA patients (25.6±3.0; p=0.044). The cognitive improvement over 24 hours was more substantial in SA patients (MMSE: 2.1±0.9; MoCA: 2.2±1.4) than in GA patients (MMSE: 0.67±1.4; MoCA: 0.67±1.8), both p<0.001. Age-based analysis showed that patients under 40 years of age had higher baseline cognitive scores and greater postoperative improvement, regardless of anesthesia type (p<0.001).

**Conclusion:** Compared with GA, SA was associated with a faster and more pronounced postoperative recovery of cognitive function. These findings suggest that SA may be preferable for reducing early cognitive impairment, particularly among older patients. Long-term follow-up is needed to confirm these effects.

**Keywords:** Postoperative cognitive dysfunction, general anesthesia, spinal anesthesia, cognitive recovery, extremity surgery

## Introduction

Postoperative cognitive dysfunction (POCD) manifests in some patients after surgery, causing transient or persistent cognitive deficits (1). The incidence of POCD is influenced by several factors, including the type of anesthesia administered, the nature of the surgical procedure, the patient's age and overall health status (2). Various anesthetic techniques, such as general and spinal anesthesia (SA), have distinct effects on cognitive function (3). While general anesthesia (GA) is often associated with an elevated risk of POCD due to its widespread effects on the central nervous system, SA may mitigate this risk (4). Consequently, in surgeries involving more localized areas, such as extremity procedures, it becomes crucial to conduct a more thorough evaluation of how different anesthesia modalities influence cognitive function.

Evaluating cognitive function following surgical interventions is crucial for healthcare professionals to optimize patient outcomes. Postoperative cognitive impairment can significantly diminish a patient's quality of life and extend the recovery period (5). Moreover, such impairment could hinder a patient's ability to resume daily activities and potentially result in long-term neurological consequences. Therefore, enhancing our understanding of how different types of anesthesia affect cognitive function is essential. This knowledge will enable healthcare professionals to make more informed decisions when selecting anesthetic methods for surgeries (6). Recent studies have yielded critical insights into the distinct impacts that various anesthetics can have on cognitive performance.

Findings from various studies indicate that elderly patients and those with comorbidities are at heightened risk of developing POCD following GA (7).

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Although SA is generally believed to mitigate these risks, further clinical data are necessary to establish more conclusive evidence. Moreover, the standardization of cognitive assessment tools and the duration of follow-up are essential to ensure consistent results in future research. The primary objective of this study was to compare the incidence and severity of POCD in patients undergoing extremity surgery under GA vs. SA.

## Methods

### Scope of the Study and Participants

This study was a randomized prospective cohort study conducted between November 2016 and April 2017 at İstanbul Training And Research Hospital. The primary objective was to evaluate and compare the effects of general and SA on cognitive function following elective extremity surgeries. A total of 60 participants were enrolled, with 30 assigned to the GA group (Group General) and 30 to the SA group (Group Spinal). Participants who met the eligibility criteria were aged 18-65 years and categorized as the American Society of Anesthesiologists (ASA) I or II according to ASA physical status classification system. Patients with diabetes or those meeting any of the exclusion criteria were omitted from the study. The exclusion criteria encompassed patients classified as ASA III or IV; those undergoing emergency surgery; patients younger than 18 or older than 65 years; patients diagnosed with neuropsychiatric disorders (e.g., Alzheimer's or Parkinson's disease); patients with alcohol dependence or chronic use of opioids or sedatives; and patients with known allergies to any medications used in the study. The study included patients undergoing elective lower extremity orthopedic surgeries, specifically involving the knee, ankle, and foot. To ensure homogeneity, only lower-extremity procedures were considered; upper-extremity procedures were excluded from the study. Ethical approval for the study was granted by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (decision number: 872, date: 11.11.2016). Furthermore, informed consent was secured from all participants or their legal representatives before enrollment.

### Data Collection and Evaluation

Within the scope of this study, patients' cognitive functions were assessed at 0 hours (preoperative) and at 4 and 24 hours postoperatively using the Mini-Mental State Examination (MMSE) (8) and the Montreal Cognitive Assessment (MoCA) (9). These cognitive tests, both validated in Turkish, were utilized for their efficiency and reliability in evaluating cognitive performance. They specifically measured domains such as attention, memory, executive functions, and abstract reasoning. Additionally, vital signs (including pulse, blood pressure and oxygen saturation) were monitored during anesthesia. Patient demographic data were recorded. Educational status was evaluated based on the total number of years of formal education as self-reported by the patients on the preoperative assessment form. This information was recorded as a continuous variable and was taken into account as a potential covariate in the interpretation of cognitive test results such as MoCA and MMSE.

Randomization was conducted using a sealed-envelope method. Prior to surgery, each patient was randomly assigned, using prepared, numbered envelopes, to either the GA group or the SA group. The study was single-blind; assessors who administered the cognitive tests were blinded to patients' group allocation.

### Anesthesia Procedures

During induction of GA, patients received propofol 2-3 mg/kg (Propofol 200 mg, Türkiye), fentanyl 1-2 mcg/kg (Talinat 0.5 mg/10 mL, VEM, Türkiye), and rocuronium 0.6 mg/kg (Esmeron 50 mg/5 mL, MSD, Greece). To maintain anesthesia, sevoflurane (Sevoflurane, Abbott, Türkiye) was administered with a carrier gas mixture comprising 50% oxygen ($O_2$) and 50% nitrous oxide at a total flow rate of 4 L/min. Muscle relaxation was sustained through maintenance doses of 0.1 mg/kg rocuronium, which were administered intravenously as necessary. For pain management, patients received 1 mg/kg of tramadol hydrochloride at 45 minutes. Prior to extubation, reversal of neuromuscular blockade was achieved using 0.04 mg/kg neostigmine (Neostigmin, Adeka, Türkiye) in conjunction with 0.02 mg/kg atropine (Atropin, Galen, Türkiye). SA was administered under aseptic conditions at the L3-L4 intervertebral space using a 25G Quincke spinal needle. A total of 3 mL of 0.5% hyperbaric bupivacaine (Marcaine Spinal Heavy, AstraZeneca, Türkiye) was injected into the subarachnoid space. In all patients, the sensory block reached the T10 dermatome, which was sufficient for the surgical procedure. Cognitive evaluations were conducted preoperatively on the morning of surgery, with follow-up assessments at 4 and 24 hours postoperatively. No intraoperative sedation was administered to patients in the SA group. All patients were monitored undera spinal block and remained fully conscious throughout the surgical procedure; no sedative agents were administered.

### Statistical Analysis

The statistical analysis of the collected data in this study was conducted using SPSS (Statistical Package for the Social Sciences) version 27.0. Continuous variables were represented as mean ± standard deviation, whereas categorical variables were reported as frequencies and percentages (%). The assessment of normality for the parameters was performed using the Kolmogorov-Smirnov test. To compare the two groups, the independent-samples t-test was applied to parameters that followed a normal distribution, whereas the Mann-Whitney U test was applied to those that did not. A p value below 0.05 was deemed to indicate statistical significance. The analyses compared the groups that received GA with those that received SA.

## Results

The mean age of the patients included in the study was 44.2±12.1 years. The gender distribution showed that 50.0% (n=30) of participants were female. Table 1 shows patient characteristics and demographic features. The mean MoCA score was 20.9±2.6 preoperatively, 21.2±3.6 at 4 hours postoperatively, increasing to 22.3±3.5 by 24 hours postoperatively. Similarly, the mean MMSE score was 24.5±2.4 at 0 hours, rising to 24.8±3.0 at 4 hours postoperatively, and further increasing to 25.9±2.7 at 24 hours postoperatively (Table 2).

No statistically significant differences were observed between the general and SA groups with respect to age, gender distribution, ASA classification, education level, or surgical duration (Table 3).

The comparison of MoCA scores between the general and SA groups revealed no significant difference at 0 hours (general: 21.3±2.8; spinal: 20.5±2.2; p=0.279). However, the SA group demonstrated significantly higher scores at 4 hours postoperatively (spinal: 21.6±2.6; general: 20.8±4.4; p<0.001) and at 24 hours (spinal:22.7±2.8; general: 22.0±4.2; p=0.001). The 4-hour MoCA score difference indicated an increase in the spinal group (1.03±1.4), whereas it indicated a decrease in the GA group (-0.53±2.0; p<0.001). At 24 hours, the spinal group exhibited a more pronounced improvement (2.2±1.4) compared to the GA group (0.67±1.8, p<0.001). These findings suggest superior cognitive recovery in the SA group (p<0.001; Table 4).

Preoperatively, the mean MMSE score in the GA group was 25.0±2.3, compared with 24.1±2.3 in the SA group (p=0.132). At 4 hours postoperatively, there was no significant difference between groups (general: 24.4±3.2; spinal: 25.2±2.8; p=0.268). At 24 hours, the SA group exhibited a slightly higher MMSE score (26.1±2.3) than the GA group (25.6±3.0, p=0.044). The 4-hour change in MMSE score showed a decrease in the GA group (-0.57±1.7) and an increase in the spinal group (1.2±1.1); this difference was statistically significant (p<0.001). Similarly, at 24 hours, the spinal group showed a greater improvement (2.1±0.9) than the general group (0.67±1.4; p<0.001) (Table 5).

Among male patients, the mean MoCA score at 0 hours was significantly higher in the GA group (22.1±2.7) than in the SA group (20.9±1.7; p=0.047).

**Table 1. Patient demographics and surgical data**

| | | Mean ± SD/count | Column, n% |
|---|---|---|---|
| **Age (year)** | | 44.2±12.1 | |
| **Gender (female)** | | 30 | 50.0 % |
| **ASA classification** | 1 | 41 | 68.3 % |
| | 2 | 19 | 31.7 % |
| **Education (year)** | | 7.9±3.4 | |
| **Surgical duration** | | 82.0±12.3 | |

The data in the table are presented as standard deviations or counts (percentages). SD: Standard deviation, ASA: American Society of Anesthesiologists

**Table 2. Cognitive test scores at different time points of all patients**

| | Mean ± SD |
|---|---|
| MoCA (0 hour) | 20.9±2.6 |
| MoCA (4 hour) | 21.2±3.6 |
| MoCA (24 hour) | 22.3±3.5 |
| MMS (0 hour) | 24.5±2.4 |
| MMS (4 hour) | 24.8±3.0 |
| MMS (24 hour) | 25.9±2.7 |

Data in the table are given as deviation or count (percentage). MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, SD: Standard deviation

**Table 3. Comparison of demographic and surgical characteristics between general and spinal anesthesia groups**

| | | General (n=30) | Spinal (n=30) | p value |
|---|---|---|---|---|
| Age (years) | | 43.0±12.9 | 44.6±12.0 | 0.605 |
| Gender | Female | 15 (50.0) | 15 (50.0) | 1.00 |
| | Male | 15 (50.0) | 15 (50.0) | |
| ASA classification | 1 | 19 (63.3) | 22 (73.3) | 0.405 |
| | 2 | 11 (36.7) | 8 (26.7) | |
| Education (year) | | 8.2±3.7 | 7.5±3.2 | 0.510 |
| Surgical duration | | 81.7±13.7 | 82.3±11.0 | 0.836 |

The data in the table are given as the standard deviation or count (percentage). ASA: American Society of Anesthesiologists

**Table 4. Comparison of MoCA scores between general and spinal anesthesia groups**

| | General (n=30) | Spinal (n=30) | |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | p value |
| **MoCA (0 hour)** | 21.3±2.8 | 20.5±2.2 | 0.279[a] |
| **MoCA (4 hour)** | 20.8±4.4 | 21.6±2.6 | **<0.001[b]** |
| **MoCA (24 hour)** | 22.0±4.2 | 22.7±2.8 | **0.001[a]** |
| **MoCA (4-hour time difference)** | -0.53±2.0 | 1.03±1.4 | **<0.001[a]** |
| **MoCA (24-hour time difference)** | 0.67±1.8 | 2.2±1.4 | **<0.001[b]** |
| **MoCA change** | | <0.001 | |

The data in the table are given as deviation or count (percentage). [a]Independent sample t-test, [b]Mann-Whitney U test. Statistically significant p values are indicated in bold. MoCA: Montreal Cognitive Assessment, SD: Standard deviation

**Table 5. Comparison of MMS scores between general and spinal anesthesia group**

| | General (n=30) | Spinal (n=30) | |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | p value |
| **MMS (0 hour)** | 25.0±2.3 | 24.1±2.3 | 0.132[a] |
| **MMS (4 hour)** | 24.4±3.2 | 25.2±2.8 | 0.268[b] |
| **MMS (24 hour)** | 25.6±3.0 | 26.1±2.3 | **0.044[a]** |
| **MMS (4-hour time difference)** | -0.57±1.7 | 1.2±1.1 | **<0.001[a]** |
| **MMS (24-hour time difference)** | 0.67±1.4 | 2.1±0.9 | **<0.001[b]** |
| **MMS change** | | <0.001 | |

The data in the table are given as deviation or count (percentage). [a]Independent sample t-test, [b]Mann Whitney U test. Statistically significant p values are indicated in bold. SD: Standard deviation, MMSE: Mini-Mental State Examination

**Table 6. Cognitive scores of male patients undergoing general and spinal anesthesia**

| | General (n=15) | Spinal (n=15) | |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | p value |
| MoCA (0 hour) | 22.1±2.7 | 20.9±1.7 | **0.047[a]** |
| MoCA (4 hour) | 22.2±4.4 | 22.2±2.1 | 0.996[b] |
| MoCA (24 hour) | 23.5±4.3 | 23.7±1.6 | 0.867[a] |
| MMS (0 hour) | 25.9±2.0 | 24.7±2.2 | **0.042[a]** |
| MMS (4 hour) | 25.7±2.9 | 25.8±2.4 | 0.89[b] |
| MMS (24 hour) | 26.8±2.8 | 26.7±1.8 | 0.938[a] |

The data in the table are given as deviation or count (percentage). [a]Independent sample t test, [b]Mann Whitney U Test. Statistically significant p values are indicated in bold. MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, SD: Standard deviation

At 4 hours, the two groups had identical mean MoCA scores (22.2±4.4 in the general group and 22.2±2.1 in the spinal group; p=0.996). At the 24-hour mark, no statistically significant difference was observed between the groups (general: 23.5±4.3, spinal: 23.7±1.6, p=0.867). Regarding MMS scores at 0 hours, the GA group showed a higher score (25.9±2.0) than the spinal group (24.7±2.2; p=0.042). At 4 and 24 hours, there were no significant differences between the groups: general: 25.7±2.9 vs. spinal: 25.8±2.4 (p=0.891) and general: 26.8±2.8 vs. spinal: 26.7±1.8 (p=0.938), respectively (Table 6).

For female patients, the mean MoCA score at 0 hours was 20.6±2.9 in the GA group and 20.2±2.6 in the SA group, with no significant difference (p=0.695). At 4 hours, the SA group had a significantly higher MoCA score (20.9±2.9) than the GA group (19.4±3.9; p=0.038). At 24 hours, there was no significant difference between the two groups (general: 20.5±3.7, spinal: 21.7±3.4, p=0.360). Regarding MMS scores, at 0 hours, the GA group had a score of 24.1±2.4, and the spinal group had a score of 23.5±2.4 (p=0.549). At 4 hours, there was no significant difference (general: 23.1±3.0, spinal: 24.7±3.2, p=0.185). After 24 hours, the GA group had a score of 24.5±2.9 and the SA group had a score of 25.5±2.7, with no significant difference (p=0.301) (Table 7).

Among patients aged <40 years, the GA group had a mean MoCA score of 23.5±2.3 at 0 hours, significantly higher than that of patients aged ≥40 years (20.1±2.3, p<0.001). Similarly, in the SA group, the <40 age group had a higher score (22.3±2.1) than the ≥40 age group (19.8±1.8, p<0.001). At 4 hours, the MoCA scores for the <40 age group were 24.3±3.3 for GA and 23.7±2.7 for SA; both were significantly higher than those of the ≥40 age groups (18.8±3.6, p<0.001 for GA; 20.7±2.0, p<0.001 for SA). The same pattern persisted at 24 hours (general: 25.5±3.2 for <40 vs. 20.0±3.3 for ≥40, p<0.001; spinal: 24.7±2.4 for <40 vs. 21.9±2.5 for ≥40, p<0.001). The MMS scores followed a similar trend. At 0 hours, participants aged <40 years in the GA group had a mean MMS score of 26.8±1.8, which was higher than that of participants aged ≥40 years (23.9±1.9; p<0.001). In the SA group, the <40 year age had a score of 26.0±2.4, while the ≥40 year group scored 23.3±1.8 (p<0.001). At 4 hours, MMS scores remained higher in the <40 group for both GA (27.3±2.6 vs. 22.7±2.1, p<0.001) and SA (27.1±2.9 vs. 24.4±2.4, p<0.001). At 24 hours, the same pattern was observed, with significantly higher scores in the <40 group for both anesthesia types (general: 28.5±2.3 vs. 24.0±1.9, p<0.001; spinal: 27.6±2.3 vs. 25.5±2.1, p<0.001) (Table 8).

**Table 7. Cognitive scores of female patients undergoing general and spinal anesthesia**

| | General (n=15) | Spinal (n=15) | |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | **p value** |
| MoCA (0 hour) | 20.6±2.9 | 20.2±2.6 | 0.695[a] |
| MoCA (4 hour) | 19.4±3.9 | 20.9±2.9 | **0.038[b]** |
| MoCA (24 hour) | 20.5±3.7 | 21.7±3.4 | 0.360[a] |
| MMS (0 hour) | 24.1±2.4 | 23.5±2.4 | 0.549[a] |
| MMS (4 hour) | 23.1±3.0 | 24.7±3.2 | 0.185[b] |
| MMS (24 hour) | 24.5±2.9 | 25.5±2.7 | 0.301[a] |

The data are given in the table mean ± standard as deviation or count (percentage). [a]Independent sample t-test, [b]Mann Whitney U test. Statistically significant p values are indicated in bold. MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, SD: Standard deviation

## Discussion

In our study, significant differences in cognitive function were observed between the general and SA groups. Postoperative cognitive recovery was faster and more effective in patients receiving SA. Notably, during the early postoperative period, particularly at the 4- and 24-hour assessments, the SA group exhibited a more pronounced improvement in cognitive performance. Age-based analyses revealed that patients under 40 years of age demonstrated superior cognitive performance in both the general- and SA groups. Additionally, gender-based comparisons indicated that male patients experienced a greater cognitive decline following GA. These findings suggest that SA more effectively preserves postoperative cognitive function, and that demographic factors may influence cognitive recovery. In our study, individuals under the age of 40 demonstrated higher cognitive test scores, underscoring the influence of age on the development of POCD. The literature frequently emphasizes the impact of age on cognitive reserve. With advancing age, mechanisms such as increased neuroinflammation, reduced neuronal plasticity, and heightened oxidative stress are believed to impair cognitive recovery in older adults. These pathophysiological processes align with our findings,

**Table 8. Cognitive scores by age group (<40 and ≥40) for general and spinal anesthesia**

| | General (n=30) | | | Spinal (n=30) | | |
|---|---|---|---|---|---|---|
| | **<40 age (n=9)** | **≥40 age (n=21)** | | **<40 age (n=11)** | **≥40 age (n=19)** | |
| | **Mean ± SD** | **Mean ± SD** | **p value** | **Mean ± SD** | **Mean ± SD** | **p value** |
| MoCA (0 hour) | 23.5±2.3 | 20.1±2.3 | **<0.001[a]** | 22.3±2.1 | 19.8±1.8 | **<0.001[a]** |
| MoCA (4 hour) | 24.3±3.3 | 18.8±3.6 | **<0.001[b]** | 23.7±2.7 | 20.7±2.0 | **<0.001[b]** |
| MoCA (24 hour) | 25.5±3.2 | 20.0±3.3 | **<0.001[a]** | 24.7±2.4 | 21.9±2.5 | **<0.001[a]** |
| MMS (0 hour) | 26.8±1.8 | 23.9±1.9 | **<0.001[a]** | 26.0±2.4 | 23.3±1.8 | **<0.001[a]** |
| MMS (4 hour) | 27.3±2.6 | 22.7±2.1 | **<0.001[b]** | 27.1±2.9 | 24.4±2.4 | **<0.001[b]** |
| MMS (24 hour) | 28.5±2.3 | 24.0±1.9 | **<0.001[a]** | 27.6±2.3 | 25.5±2.1 | **<0.001[a]** |

The data are given in the table mean ± standard as deviation or count (percentage). [a]Independent sample t-test, [b]Mann Whitney U test. Statistically significant p values are indicated in bold. MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, SD: Standard deviation

particularly the more favorable cognitive recovery observed in patients aged ≥40 years who received SA.

O'Brien et al. (10) compared the incidence of delirium between patients with and without cognitive impairment after undergoing either general or SA. The findings indicated that the incidence of delirium did not differ significantly between the two anesthesia methods; both groups exhibited comparable rates. Additionally, delirium severity, in-hospital complications, and functional recovery were comparable between general and SA. In contrast, Silbert et al. (3) examined POCD and found a higher incidence in the SA group than in the GA group, particularly at the 3-month follow-up. However, this difference was not statistically significant. Consistent with the findings of Ehsani et al. (7), our study demonstrated a higher prevalence of cognitive impairment among patients who underwent GA. In both studies, SA was shown to preserve cognitive function better. The association between cognitive impairment and factors such as age, ASA classification, and gender, as identified by Ehsani et al. (7), aligns with the results of our research. These findings suggest that GA may have a more detrimental impact on cognitive function.

Konishi et al. (11) examined the effects of sevoflurane and propofol used in anesthesia maintenance on POCD and found in the incidence of POCD between the two drugs. This finding suggests that the development of POCD may be influenced by factors other than the specific anesthetic agents used. However, in our study, notable differences in cognitive recovery were observed between GA and SA. Cognitive function improved more rapidly and was better preserved in patients who received SA compared to those who underwent GA. Anwer et al. (12) investigated the effects of general and SA on postoperative cognitive function in young adults and elderly patients, and found that GA led to cognitive impairment in elderly patients. In our study, patients were categorized into groups using an age threshold of 40 years. While Anwer's study defined elderly patients as those aged ≥60 years, our use of a 40-year age threshold provides a different perspective. Although age 60 is conventionally used as the cut-off in most cognitive function studies, we selected 40 years as the threshold to provide an alternative perspective and explore possible cognitive changes in earlier adulthood. Furthermore, this threshold ensured balanced subgroup sizes for valid statistical comparisons. Our results indicate that GA has a more detrimental effect on cognitive function in patients over 40 years of age. In contrast, cognitive recovery was more pronounced in patients older than 40 years who received SA. The findings of Anwer et al. (12), which demonstrated that GA caused cognitive impairment in elderly patients, are consistent with our findings in patients over 40 years of age.

Zhang et al. (13) compared spinal vs. GA in 80 elderly orthopedic patients and found that SA resulted in faster recovery, improved cognitive outcomes, and fewer cases of POCD. Tzimas et al. (14) examined the effects of general vs. SA in hip fracture surgery, reporting no significant differences in most cognitive tests but a higher incidence of delirium in the spinal group (27% vs. 12% in the general group). Ezhevskaya et al. (15) analyzed 48 patients undergoing thoracolumbar fusion and showed that combined epidural and GA reduced pain, inflammation, immune dysfunction, and POCD compared with GA alone. Aytaç et al. (16) compared MMSE and MoCA scores among elderly patients undergoing inguinal herniorrhaphy and found that postoperative MoCA scores were significantly lower in both anesthesia groups, while the GA group showed a significant decrease in MMSE scores. The incidence of POCD was higher when using the MoCA (32.9%) than when using the MMSE (15.2%). Our study integrates these findings by exploring the cognitive and functional impacts of different types of anesthesia, aiming to clarify the role of anesthesia in POCD and to optimize postoperative outcomes in elderly patients.

### Study Limitations

Our study has some limitations. First, postoperative cognitive function was evaluated only within the first 24 hours after surgery. This limits the ability to fully investigate the likelihood and long-term effects of POCD. A longer follow-up period may have been beneficial in assessing the long-term effects of POCD. Moreover, the limited sample size in this study may affect the extent to which the findings can be generalized to a larger population. Furthermore, the selection of anesthesia type was based on the anesthesiologist's discretion, a factor that was not accounted for within the study. This means that the selection of anesthesia was not randomized, which could introduce bias. Additionally, discharge time was not assessed, which may have provided further insight into the overall postoperative recovery process.

## Conclusion

The findings of this study indicate that SA facilitates early postoperative cognitive recovery in patients undergoing extremity surgery compared with GA. Individuals in the SA group demonstrated significantly higher MMSE and MoCA scores at both 4- and 24-hour postoperative assessments, indicating a lower risk of postoperative cognitive decline. Age also influenced cognitive outcomes: younger patients (<40 years) recovered better regardless of anesthesia type, whereas older patients were more affected by GA. Although the study was limited by a small sample size and a short follow-up period, these findings suggest that SA may be preferable for reducing early POCD. Further studies are needed to confirm long-term effects. As our study focused primarily on cognitive outcomes, validated patient-reported outcome measures, such as the Quality of Recovery-40, were not utilized. However, future research incorporating such tools may offer a more comprehensive assessment of both cognitive recovery and patient satisfaction with anesthesia techniques.

### Ethics

**Ethics Committee Approval:** Ethical approval for the study was granted by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (decision number: 872, date: 11.11.2016).

**Informed Consent:** It was secured from all participants or their legal representatives before enrollment.

**Footnotes**

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

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# Body Packing: Clinical Outcomes and Management Approaches in A Tertiary Referral Center

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## ABSTRACT

**Introduction:** Body packing, the internal concealment of illicit drugs within the gastrointestinal tract, remains a significant public health and medicolegal concern. Advances in drug-packet manufacturing have reduced rupture rates but have not eliminated the risk of life-threatening complications, including acute toxicity, bowel obstruction, and perforation. Early detection and optimal management are critical to preventing morbidity and mortality.

**Methods:** We conducted a retrospective observational study of patients admitted to the Department of Emergency, University of Health Sciences Türkiye, Çam and Sakura City Hospital, between June 2021 and July 2025 with confirmed body packing. The diagnosis was established by plain abdominal radiography (X-ray) and non-contrast abdominopelvic computed tomography (CT). Patients were classified into two groups: those managed conservatively and those requiring additional intervention (endoscopic or surgical). Demographic, clinical, laboratory, and imaging data were analyzed to identify predictors of conservative management failure.

**Results:** Of 45 hospitalized patients, 36 met inclusion criteria. The majority were male (86%), and the mean age was 36.0±11.6 years. X-ray imaging detected packets in 88.9% of cases, whereas non-contrast CT detected them in 100% of cases. Conservative management was successful in 30 patients (83.3%). Six patients (16.7%) required intervention -three endoscopic and three surgical. The surgical intervention rate was 8.3%, with one intraoperative death (2.7%). Complication and toxicity rates were 16.7% and 8.3%, respectively. Predictors of intervention included fewer ingested packets (p=0.03), longer hospital stay (p=0.005), presence of symptoms (p=0.02), positive physical examination findings (p=0.01), and electrocardiography abnormalities (p=0.01).

**Conclusion:** Non-contrast CT is the gold standard for detecting and quantifying drug packets in body packers, offering 100% diagnostic accuracy in this cohort. Conservative management is safe and effective in the majority of patients; however, close monitoring is essential in symptomatic patients, those with abnormal findings on physical examination, or those with prolonged ingestion-to-admission intervals. Surgical intervention should be reserved for cases with toxicity, bowel obstruction, or failed conservative management.

**Keywords:** Body packing, drug smuggling, gastrointestinal obstruction, acute cocaine toxicity, drug trafficking

## Introduction

Drug trafficking continues to represent a significant global concern, with an ongoing evolution of sophisticated techniques aimed at evading detection by law enforcement authorities. The terms “bodypacker” and “mule” refer to individuals who internally conceal illicit substances -most commonly heroin or cocaine- within small rubber or latex packages to transport them across international borders (1). These packages are typically ingested and retained in the gastrointestinal tract, although rectal or vaginal insertion is also employed (2). The first documented account of internal drug smuggling through ingestion or insertion into body cavities was published by Mebane and DeVito (3) in 1975.

Since the initial publication of that case report, substantial changes have occurred in both the clinical presentation and management of these patients -primarily driven by advancements in the packaging techniques used for drug concealment. Traditionally used materials -such as cocaine-filled latex gloves, balloons, and condoms- have largely been replaced by mechanically manufactured, multilayered latex containers that are meticulously sealed (4,5). These improvements have significantly reduced the risk of package rupture, leading to a marked decrease in associated morbidity and mortality. Nevertheless, the intraluminal transport of cocaine pellets via body-packing continues to pose serious medical risks, including acute cocaine toxicity, intestinal obstruction, and gastrointestinal perforation (6).

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Historically, Türkiye has functioned as a critical transit hub in global drug trafficking networks, particularly for heroin originating in Afghanistan and transported to European destinations via Iran and Türkiye -along a route widely known as the "Balkan corridor." According to the United Nations World Drug Report 2024, Iran and Türkiye were identified as the two countries with the largest quantities of illicit drugs seized, with Türkiye ranking highest for cocaine confiscations (7). At the national level, this has led to a marked increase in arrests associated with cocaine transportation, most notably in İstanbul, the country's largest city and home to its principal international airport (8). Owing to its close proximity to the airport, our hospital has emerged as a primary referral center for the management of such cases. As a result, our institution has acquired substantial clinical expertise in treating this unique patient population.

This population of "travelers" poses an emerging and increasingly complex challenge for a diverse group of medical specialists in Türkiye, including emergency physicians, internists, surgeons, radiologists, and clinical toxicologists. The clinical management of individuals internally transporting drug packets represents a recurring medical issue, yet many healthcare professionals remain unfamiliar with this distinct patient cohort and the associated diagnostic and therapeutic complexities. In light of the increasing number of body packers apprehended upon arrival in İstanbul, this study aimed to evaluate the clinical outcomes of conservative management and to determine the indications for non-conservative intervention among patients treated at our tertiary referral center for detained individuals.

## Methods

### Patients and Data Collection

This retrospective observational study included individuals admitted to the Department of Emergency, University of Health Sciences Türkiye, Çam and Sakura City Hospital, between June 2021 and July 2025 and who were consulted by the General Surgery Department following a diagnosis of body-packing. The study was approved by the local Ethics Committee of the University of Health Sciences Türkiye, Çam and Sakura City Hospital (decision number: KAEK/03.09.2025.332, date: 22.09.2025).

Individuals suspected of body-packing, typically apprehended by law enforcement upon arrival at İstanbul International Airport, were transferred to our emergency department for further evaluation. All such cases underwent a standardized diagnostic approach including X-ray and computed tomography (CT) scans to confirm or rule out the presence of intraluminal drug pellets. During the study period, 45 patients suspected of body-packing were admitted to our institution. Of these, nine patients in whom imaging studies (X-ray and CT) identified no packets were excluded. Thus, 36 confirmed body-packing cases were included in the final analysis. A diagnosis of body-packing was established either by the radiological identification of drug-containing packets or by direct observation of packet excretion. Once confirmed to be without complications, patients were either admitted to a general ward or managed in the short-stay unit of the emergency department. The primary goals of inpatient management were to facilitate the safe and complete evacuation of all ingested drug packets and to monitor for potential complications, particularly drug toxicity from ruptured packets or intestinal obstruction from impacted packets. During hospitalization, all patients were continuously supervised by law enforcement officers, who collected expelled packets and performed on-site presumptive drug tests to identify the type of illicit substance involved.

All suspected body-packers were evaluated using a standardized protocol in the emergency department, which included initial imaging, typically X-ray and CT, to determine the number and anatomical distribution of the foreign bodies and routine blood investigations. Conservative management strategies included bowel rest and close clinical observation, with serial X-rays and, when necessary, CT scans performed to monitor progression until the packets were fully cleared. Gastrointestinal motility was promoted through the administration of laxatives or enemas to minimize the transit time of drug packets through the gastrointestinal tract. Patients exhibiting any of the following clinical features were monitored more intensively daily: gastrointestinal symptoms (e.g., abdominal pain, signs of bowel obstruction, or suspected gastrointestinal perforation) or manifestations of drug intoxication.

Once a patient was confirmed as a body packer, electronic medical records were reviewed to collect data on demographics, clinical characteristics, laboratory results, the total number of packets ingested, and therapeutic measures employed, including laxative administration, gastrointestinal decontamination procedures, endoscopic retrieval, and surgical intervention. Furthermore, all X-rays and CT scans obtained at admission and during the hospital stay were reassessed as part of the study protocol.

Failure of conservative management was defined as the need for any non-conservative intervention, including endoscopic or surgical procedures, based on one or more of the following criteria: (1) radiological or clinical evidence of gastrointestinal obstruction (e.g., persistent vomiting, abdominal distension, or absence of bowel movements for more than 48 hours), (2) signs of drug intoxication or toxicity suggestive of packet rupture (e.g., tachycardia, hypertension, agitation, or altered mental status), or (3) radiological evidence of retained or ruptured packets despite adequate conservative measures, such as administration of laxatives or enemas.

### Statistical Analysis

Patients were classified into two groups: conservative management and additional intervention. Continuous variables were summarized as mean ± standard deviation and compared using the Student's t-test. Non-normally distributed continuous variables were analyzed using the Mann–Whitney U test. Categorical variables were summarized as counts and percentages and compared using the chi-square test; Fisher's exact test was used when any expected cell frequency was <5. Two-tailed p-values $<0.05$ were considered statistically significant. Statistically significant differences were marked with an asterisk (*) in the results table. Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

## Results

During the study period, 45 body packers were hospitalized. Among these patients, nine who had no foreign body detected by X-ray or CT during the initial examinations were excluded from the study. Of these patients, 86% were male, with a median age of 36 years (range: 19-61). Interventions included an initial X-ray + CT and an osmotic laxative with monitoring an average of 4.02 days. Abdominal X-ray imaging was diagnostic in 32 (88.9%) patients, and CT was diagnostic in all patients (100%). Conservative treatment was successful in 30 patients (83.3%). Demographic and clinical characteristics of the patients are summarized in Table 1.

Conservative management failed in 6 (16.7%) of the 36 patients. Among them, three patients underwent endoscopic intervention and three required surgery; in one case, an endoscopic intervention was attempted but proved unsuccessful and was followed by surgery. Endoscopic intervention was successful in one patient with gastric outlet obstruction, achieving complete removal of the obstructing capsules. In a second case, ruptured packets led to severe drug intoxication with multiorgan failure; bedside endoscopic removal was successful following intensive care unit (ICU) admission and hemodialysis. In the third case, the patient, who presented with symptoms of drug intoxication and was resuscitated in the ICU, underwent an attempted bedside endoscopy. However, the procedure was unsuccessful because the packets were excessively large. Surgical intervention was subsequently planned, but the patient experienced cardiac arrest intraoperatively. Among the three patients who underwent surgery, one died intraoperatively, as mentioned above. Another patient presented with drug intoxication and imaging evidence of multiple drug packets extending from the stomach to the cecum, with associated intestinal obstruction. Laparotomy revealed gastric outlet obstruction and two additional packets in the distal ileum, which were all removed via gastrotomy and enterotomy. A ruptured cecal packet was also noted. The patient recovered uneventfully after follow-up in the ICU and ward, experienced transient postoperative hyperamylasemia and hyperlipasemia that resolved with supportive care, and was discharged on postoperative day 12. The third surgical case involved a patient initially managed conservatively after ingesting 38 capsules. On day 18, surgery was performed for persistent gastric outlet obstruction, and one capsule was removed via gastrotomy. The patient was discharged on postoperative day 4 without complications.

Comparison between the conservatively managed and non-conservative groups revealed several significant differences. Patients in the non-conservative group had a longer mean follow-up period (10.00±8.07 days vs. 2.83±1.02 days, p=0.005) and ingested fewer capsules on average (24.50±18.12 capsules vs. 48.60±24.76 capsules, p=0.03). Additionally, the presence of symptoms at admission, positive physical examination findings, and electrocardiographic abnormalities were significantly more common among patients requiring intervention (50% vs. 6.7%, p=0.02; 50% vs. 3.3%, p=0.01; and 50% vs. 0%, p=0.01, respectively). No statistically significant differences were observed between the groups regarding age, sex distribution, or laboratory abnormalities (including white blood count, creatinine, and glucose levels) (Table 2).

## Discussion

Drug trafficking and body packing continue to pose significant global health and security challenges (9). Although modern multilayer drug packets have reduced rupture-related complications, body packing still carries risks of acute intoxication, bowel obstruction, and perforation (10,11). Early diagnosis remains essential, as plain radiography may miss non-radiopaque packets, while CT provides near-complete accuracy. Management has shifted toward conservative treatment with close observation, reserving intervention for those who develop symptoms or fail to progress (11). Despite growing case numbers, no universally accepted diagnostic algorithm exists. Most centers rely on locally developed protocols combining laboratory tests, imaging modalities, and substance analyses (12,13). This study presents our institutional experience and diagnostic–therapeutic approach in patients with

**Table 1. Demographic and clinical characteristics**

| Characteristics (n=36) | Category | Value |
|---|---|---|
| Age (year) | Mean ± SD | 36.0±11.6 (19-61) |
| Sex | Male<br>Female | 31 (86)<br>5 (14) |
| Number of ingested capsules | Median (min-max) | 40.5 (1-100) |
| Presence of symptoms (n, %) | Yes<br>No | 5 (14)<br>31 (86) |
| Positive physical exam findings (n, %) | Yes<br>No | 4 (11)<br>32 (89) |
| Conservative treatment (n, %) | Yes<br>No | 30 (83.3)<br>6 (16.7) |
| Surgical or endoscopic intervention n=6 (n, %)** | Endoscopy<br>Surgery<br>Both | 3 (50)<br>2 (33.3)<br>1 (16.7) |
| Duration of follow-up | Median (min-max) | 4.02 (1-22) |
| Abnormal laboratory finding | Yes<br>No | 2 (5.6)<br>34 (94.4) |

**Percentages are calculated within the intervention subgroup (n=6). SD: Standard deviation, Min: Minimum, Max: Maximum

**Table 2. Variables associated with conservative management failure**

| Variables | Conservative (n=30) | Non- conservative (n=6) | p value |
|---|---|---|---|
| Age (year), mean ± SD | 35.30±11.52 | 39.50±12.14 | 0.3831[a] |
| Sex, n (%)<br>Female / male | <br>4 (13.3) /26 (86.7) | <br>1 (16.7) / 5(83.3) | <br>1.000[b] |
| Follow-up period, n (day) | 2.83±1.02 | 10.00±5.07 | **0.005**[a]* |
| Number of ingested capsules (n) | 48.60±24.76 | 24.50±18.12 | **0.03**[c]* |
| Presence of symptoms at the time of admission n (%)<br>Yes<br>No | <br>2 (6.7)<br>28 (93.3) | <br>3 (50)<br>3 (50) | <br>**0.02**[b]* |
| Physical examination finding n (%)<br>Yes<br>No | <br>1 (3.3)<br>29 (96.7) | <br>3 (50)<br>3 (50) | <br>**0.01**[b]* |
| Laboratory abnormality<br>WBC<br>Creatinin<br>Glucose | <br>9.17±5.46<br>0.81±0.49<br>103.93±79.71 | <br>3.87±3.38<br>1.35±1.88<br>192.00±196.89 | <br>0.08[b]<br>0.94[b]<br>0.33[b] |
| **ECG abnormality n (%)<br>Yes<br>No | <br>0 (0)<br>30 (100) | <br>3 (50)<br>3 (50) | <br>**0.01**[b]* |

*p<0.05, [a]: Mann-Whitney U test, [b]: Fisher's exact test, [c]: Student's t-test, SD: Standard deviation, **ECG: Electrocardiography, n: number, WBC: White blood count

suspected body packing. In our cohort, failure of conservative management appeared to be associated with the presence of symptoms at admission and with radiological evidence of delayed progression, suggesting that both clinical and imaging findings play a key role in predicting the need for endoscopic or surgical intervention.

In line with previous literature suggesting that young men are often selected to transport substances due to greater physical capacity and fewer comorbidities, 86% of patients presenting to the emergency department in our cohort were male (6,14). This demographic pattern underscores the need for heightened clinical vigilance among this predominantly young male patient population.

Body packers are difficult to detect because of unreliable histories and the frequent absence of symptoms. Supine X-ray is the standard initial screening tool, offering low cost, accessibility, and a reported sensitivity ranging from 60% to 85% (12,15). If X-ray findings are inconclusive or negative but clinical suspicion remains high, current protocols recommend low-dose non-contrast CT, which delivers radiation doses comparable to those of X-ray while providing superior diagnostic accuracy (1,12,16,17). Non-contrast CT is considered the gold standard in such cases; reported sensitivity and specificity approach 100%, and it allows precise quantification of packets. Low-radiation CT protocols have been suggested to be sufficiently sensitive, although evidence remains limited (12,17). In a study of 282 patients, Bonnefoy et al. (18) reported that capsules were visualized on X-ray imaging in 98.6% of cases. Conversely, Markovits et al. (19) found a false-negative rate of 65% with X-ray imaging. Another study evaluating 189 patients suggested that the rate of false negatives may be increasing due to progressively more sophisticated packing techniques (5). In our study, consistent with previous reports, capsules were detected on X-ray imaging in 88.9% of patients, while non-contrast abdominal CT accurately confirmed or excluded the presence of packages in 100% of cases.

Conservative treatment is widely regarded as a safe approach, aiming to facilitate the spontaneous expulsion of drug packets, while reserving surgical intervention for cases in which conservative management fails or complications develop. Polyethylene glycol–electrolyte lavage solution (PEG), or lower-dose oral PEG, is commonly used for bowel cleansing in asymptomatic body packers (18). In published series, the reported proportion of body packers successfully managed with conservative treatment ranges from 70% to over 90%, depending on patient selection and institutional protocols (20-25). In six large retrospective studies involving 3.812 body packers, more than 98% were treated successfully with a conservative regimen; emergency laparotomy was required in less than 2%; and fatal outcomes were observed in only two patients (20-25). In our cohort, 83.3% of patients were treated conservatively with observation, oral purgation, and lavage, a rate consistent with previous literature. This alignment supports the safety and efficacy of conservative management when applied with appropriate clinical monitoring and the exclusion of high-risk cases.

Treatment strategies for body packers have evolved considerably over the past decades. In 1977, Suarez et al. (26) recommended surgical intervention for all patients; however, current practice favors conservative management whenever possible, usually with in-hospital observation (27). The refinement of drug-packet manufacturing techniques has contributed to a marked reduction in complication rates. Reported surgical rates vary between 2% and 24% (27-29). Schaper et al. (30) reported a mortality rate of 1.4% and a laparotomy rate of less than 1%. In a New York City cohort of 1.250 confirmed body packers evaluated between 1993 and 2005, only 4.5% required hospitalization and 2% underwent surgery (20). Veyrie et al. (21), in a study of 1.181 patients, reported that 19 patients (1.6%) underwent surgery: 13 for obstruction and 6 for acute intoxication. Bonnefoy et al. (18) found that only 3.5% of patients developed overt signs of cocaine toxicity; no cases required surgery and there were no deaths.

In our series, the surgical intervention rate was 8.3%, with an equal proportion (8.3%) undergoing endoscopy. Mortality was 2.7%, and toxicity occurred in 8.3% of patients. The overall complication rate was 16.7%. One endoscopic attempt failed, requiring conversion to surgery. All patients who required invasive intervention presented with abdominal symptoms such as nausea, vomiting, and bloating and exhibited pathological abdominal examination findings consistent with ileus, acute abdomen, or clinical or laboratory evidence of intoxication. Notably, in all such cases, the minimum time elapsed since ingestion was five days. Endoscopic removal is generally not recommended due to the risk of packet perforation. Surgical intervention is reserved for patients presenting with signs of toxicity or mechanical gastrointestinal obstruction, or for patients with persistent packet retention on prolonged follow-up (19).

### Study Limitations

This study has several limitations. First, the data were obtained through a retrospective review, which may have introduced selection and information bias. Second, toxicology and urine analyses were performed only in patients who exhibited signs of intoxication, potentially leading to underestimation of asymptomatic carriers. Third, information on the size and type of packaging of the retrieved packets was not available. Additionally, the relatively small number of patients limits the generalizability of our findings; therefore, larger prospective, multicenter studies are warranted to validate these results.

## Conclusion

The increasing incidence of body packers poses significant challenges for healthcare systems in terms of timely detection, prevention of complications, and reduction of intoxication-related mortality. Accurate diagnosis, quantification of the number of packets, and confirmation of their complete removal are essential; in this regard, CT can be considered the optimal imaging modality. While conservative management remains effective in the majority of cases, careful monitoring of the time elapsed since ingestion, the development of symptoms, and physical examination findings is critical. Maintaining high clinical vigilance among healthcare providers is essential to minimizing complications and mortality in this patient population.

### Ethics

**Ethics Committee Approval:** The study was approved by the local Ethics Committee of the University of Health Sciences Türkiye, Çam and Sakura City Hospital (decision number: KAEK/03.09.2025.332, date: 22.09.2025).

**Informed Consent:** Retrospective study.

### Footnotes

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# Descriptive Temporal and Seasonal Distribution in Peptic Ulcer Perforation: A Ten-Year Cohort Study

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## ABSTRACT

**Introduction:** Peptic ulcer perforation (PUP) is a critical condition in which gastric or duodenal ulcers rupture, leading to leakage of abdominal contents and life-threatening complications. While factors such as age, gender, smoking, and medication use are associated with PUP, a significant question remains unanswered: why does PUP often occur in patients without prior symptoms of peptic ulcer disease? Seasonal patterns, which may act as external triggers, have been underexplored in this context. This study aims to descriptively examine the monthly and seasonal distribution of PUP incidence over a ten-year period to better understand its occurrence and potential environmental influences.

**Methods:** A retrospective cohort study was conducted at a Turkish tertiary hospital, gathering data on PUP cases from January 1, 2010, to December 31, 2019. To ensure a focused cohort, we excluded patients with prior gastric surgery and included only confirmed operative cases. We collected demographic (age and gender) and clinical (perforation site and seasonal trends) data. Descriptive statistics and appropriate non-parametric tests (Kruskal-Wallis) were used to analyze patient characteristics across seasons. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies.

**Results:** Among 287 PUP patients, who were predominantly male (83.3%) with a mean age of 42.8 years, a significant seasonal imbalance was noted. PUP cases were most frequent in summer (June to August) (34.1%) and least frequent in winter (20.6%) (p=0.012). July recorded the highest number of PUP incidents, while September recorded the fewest PUP incidents. The median age also varied significantly across seasons (p=0.034), with the youngest patients observed in autumn.

**Conclusion:** This descriptive study found a significant seasonal imbalance in PUP case occurrence, with higher case frequency in summer and lower-case frequency in autumn and winter. These findings serve as descriptive evidence of PUP patterns in this cohort and warranting further analytical research into potential underlying mechanisms.

**Keywords:** Seasonal distribution, peptic ulcer disease, perforation, incidence

## Introduction

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by ulcers in the stomach or duodenum lining. Despite effective modern treatments, PUD poses health risks due to complications such as bleeding and perforation (1). While the overall prevalence of PUD has declined in recent decades due to improved management strategies, complications such as peptic ulcer perforation (PUP) remain significant clinical concerns. PUP is a life-threatening emergency that occurs when an ulcer erodes through the stomach or duodenal wall and requires immediate intervention, as it can lead to peritonitis and sepsis if untreated (2,3).

Despite advancements in medical management, including the use of proton pump inhibitors and eradication therapies for *Helicobacter pylori* (*H. pylori*), the incidence of PUP remains significant (4). As with PUD, several risk factors for PUP have been identified, including older age, male gender, smoking, non-steroidal anti-inflammatory drug (NSAID) use, and *H. pylori* infection. However, growing evidence indicates that external factors, such as seasonal variations, may also influence PUP incidence, which is the primary focus of this study.

Seasonal patterns in gastrointestinal conditions, including PUD and its complications, have been the subject of ongoing research, particularly in regions with pronounced seasonality. Seasonal variation in peptic ulcer-

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related conditions has been examined in several studies, with some reporting increased ulcer symptoms and complications in colder months, possibly owing to lifestyle changes, dietary factors and environmental stressors (5,6). While studies have examined PUD seasonality, fewer have focused specifically on PUP, and the results have been inconsistent. For example, some studies have found higher PUP rates in winter, hypothesizing that stress, medication use, or an increased incidence of respiratory infections during cold weather might exacerbate ulceration (6). Conversely, research, including the findings of the present study, has suggested an increased incidence of PUP during the summer months, possibly due to dehydration or increased outdoor activity (7).

The implications of these findings extend beyond academic interest. Recognizing seasonal patterns in the presentation of PUP cases can inform the strategic allocation of surgical and critical care resources. However, the mechanisms underlying PUP, which often occurs in patients without prior symptoms of PUD, remain poorly understood. This phenomenon raises critical questions about the role of external triggers, such as seasonal and environmental factors, in initiating a perforation in otherwise asymptomatic individuals. In this study, we aim to address these gaps by describing the seasonal distribution of PUP incidence, providing insights into potential temporal patterns, and offering preliminary evidence-based recommendations for its prevention and management. Specifically, the primary research question of this study is: What are the monthly and seasonal distributions of PUP cases over a ten-year period in a Turkish tertiary-care center cohort?

## Methods

### Study Design and Setting

This retrospective cohort study was conducted at the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, a tertiary care center in Türkiye. The study aimed to investigate the seasonal distribution of patients undergoing surgery for PUP between January 1, 2010, and December 31, 2019. Ethical approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (approval number: 2024/288, date: 05.09.2024). This study adhered to the principles of the Declaration of Helsinki and its amendments, and patient data were anonymized before analysis. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

### Patient Selection and Exclusion Criteria

The retrospective study included all patients diagnosed with PUP during the specified time period. Specifically, patients were included only if they underwent an emergency surgical procedure (laparoscopy or laparotomy) during which a PUP was visually confirmed. To ensure a homogeneous study population, patients with a history of gastric surgery, which could influence the risk of perforation, were excluded from the study. This exclusion was necessary to limit confounding factors, as prior gastric surgeries might alter the natural course of ulcer disease and affect the likelihood of perforation. All patients included in the study underwent emergency surgery for confirmed PUP. Patients in whom a perforation was not confirmed during diagnostic laparoscopy or laparotomy were excluded. As this study is descriptive, a control group of patients with non-perforated PUD was not included. Clarifying the exclusion criteria, we excluded:

- Patients with a history of any prior gastric or upper gastrointestinal surgery.
- Patients where PUP was not confirmed intraoperatively.

### Data Collection

Data were retrospectively collected from hospital registries, medical records, and surgical reports. Demographic variables, including age and gender, were obtained, along with clinical information about the site of perforation (gastric or duodenal) and the date of diagnosis or surgery. Given that seasonal patterns were a focus of the study, seasons were categorized as follows: spring (March, April, May), summer (June, July, August), autumn (September, October, November), and winter (December, January, February). This definition of the seasons aligns with the established meteorological categorization for Türkiye. The site of perforation (gastric or duodenal) was also recorded for each patient.

### Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables, such as age, were presented as mean ± standard deviation or median [interquartile range (IQR)] depending on the data distribution. Either chi-square test or Fisher's exact test was applied to categorical variables (e.g., gender and season) to assess seasonal differences in case proportions.

To compare age (a continuous variable) across the four seasonal categories, the Kruskal-Wallis one-way analysis of variance by ranks test was used because a preliminary Shapiro-Wilk test indicated that age was not normally distributed across the seasonal groups. The Kruskal-Wallis test was chosen as the appropriate non-parametric method for comparing medians across three or more independent groups. Poisson regression was used to estimate the relative risk of PUP occurrence in each season relative to the least frequent season (winter), providing further insight into the temporal imbalance in case distribution. Poisson regression was selected because of its suitability for modeling count data (the number of perforations) and comparing incidence rates over time.

All statistical tests were two-sided, and a p-value of ≤0.05 were considered statistically significant. Confidence intervals (CI) were calculated where applicable, and results were presented with 95% CI. Given limitations in the available data, no additional adjustments were made for potential confounders such as NSAID use, *H. pylori* infection, or smoking, because these variables were not systematically recorded for all patients. However, their potential impact on PUP incidence is acknowledged in the Discussion section.

## Results

### Demographic Characteristics

A total of 287 patients diagnosed with PUP were included in the study. Of these, 83.3% were male and 16.7% were female. The mean age of the overall cohort was 42.8±18.2 years (95% CI: 39.0-43.3), with an age range from 18 to 93 years. The median age was 41.0 years (IQR: 28.0-55.0). The gender distribution remained consistent across seasons, but the male-to-female ratio was highest during autumn (8.9:1) and lowest during spring (2.9:1). The distribution of perforation sites revealed that 210 patients (73.2%) had duodenal perforations, and 77 patients (26.8%) had gastric perforations. The seasonal distribution of gastric and duodenal perforations did not differ significantly (p=0.234).

### Seasonal Distribution

Seasonal analysis revealed a significant imbalance in PUP case counts, with the highest number of cases occurring in summer (34.1%), followed by spring (24%), autumn (21.3%), and winter (20.6%) (chi-square test, p=0.012). The peak in PUP incidence was observed in July, while the lowest number of cases occurred in September. This seasonal imbalance is clearly visualized in Figure 1, with detailed monthly fluctuations presented in Figure 2. Gender-specific analysis indicated a higher PUP incidence among males across all seasons, although no statistically significant gender difference in incidence was observed between seasons (p=0.119). Detailed demographic comparisons and patient characteristics by season are summarized in Table 1.

### Age Comparison and Poisson Regression Analysis

The Kruskal-Wallis test indicated a statistically significant difference in the median age of patients across the four seasonal groups (p=0.034).

Specifically, patients diagnosed with PUP in autumn were significantly younger (mean age 36.6±15.4 years; median 34.0 years) than those diagnosed in other seasons.

Poisson regression analysis demonstrated a significantly higher incidence of PUP during the summer months (June-August) (p=0.019) compared to other seasons. Regression statistics by season are shown in Table 2.

### Seasonal and Monthly Fluctuations

Notably, July consistently showed the highest monthly incidence of PUP, aligning with the overall summer peak observed in the seasonal analysis. The regression analysis results, highlighting the seasonal distribution of cases in PUP incidence, are summarized in Table 2.

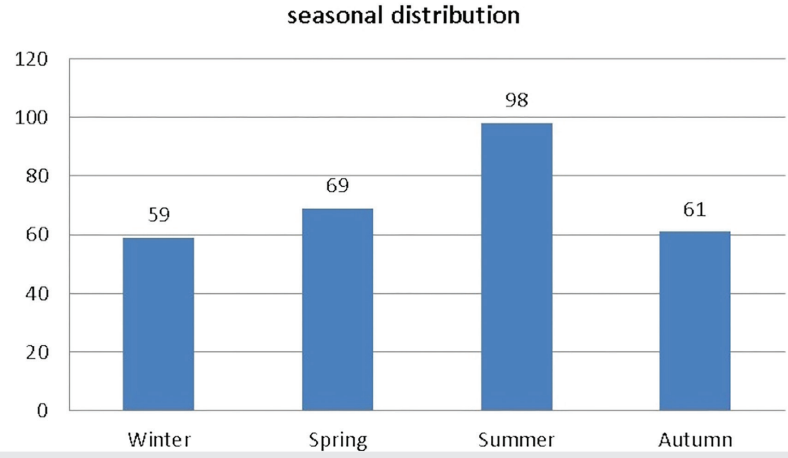


**Figure 1.** Seasonal distribution in patients with peptic ulcer perforation

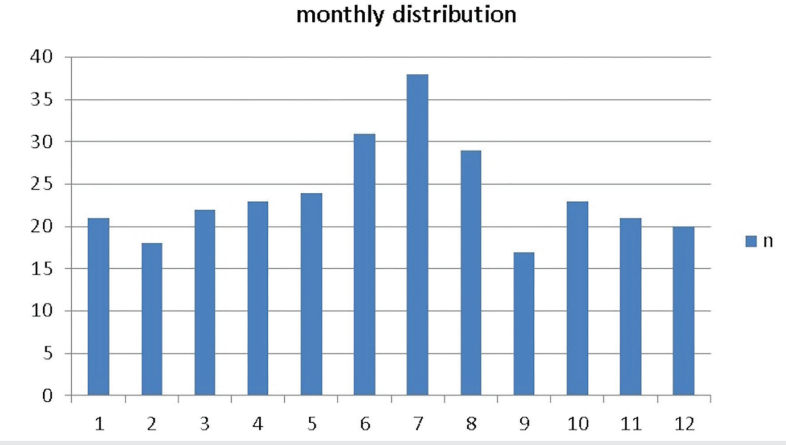


**Figure 2.** Monthly distribution in patients with peptic ulcer perforation

**Table 1. Characteristics of patients according to seasons**

| n (%) | | Total | Winter | Spring | Summer | Autumn | p value |
|---|---|---|---|---|---|---|---|
| | | 287 | 59 (20.6) | 69 (24) | 98 (34.1) | 61 (21.3) | 0.012* |
| Gender; male n (%) | | 239 (83.3) | 50 (20.9) | 51 (21.3) | 85 (35.6) | 53 (22.2) | 0.119 |
| | Female n (%) | 48 (16.7) | 9 (18.8) | 18 (37.5) | 13 (27.1) | 8 (16.7) | |
| Age | Mean (IQR) | 41.0 (28.0-55.0) | 45.0 (30.0-62.0) | 43.0 (27.0-57.0) | 43.0 (28.0-58.0) | 34.0 (25.0-48.0) | |
| | 95% CI for mean LB-UB | 39.0-43.3 | 40.3-51.6 | 38.7-47.9 | 36.6-43.3 | 32.2-40.5 | 0.034* |
| | Min-max | 18-93 | 18-93 | 19-82 | 18-89 | 18-87 | |

*p<0.05 was considered statistically significant. Age comparison test: Kruskal-Wallis. p<0.05 was considered statistically significant. IQR: Interquartile range, CI: Confidence interval, Min: Minimum, Max: Maximum, LB: lower bound, UB: upper bound

**Table 2. Poisson regression statistics by season**

| | Coefficients | Standard error | t-value | p value | Lower-upper 95 % |
|---|---|---|---|---|---|
| Intercept | 6.301 | 1.364 | 4.621 | 0.000 | 3.520-9.082 |
| Time-period | -0.018 | 0.051 | -0.347 | 0.731 | -0.122-0.086 |
| Spring | 0.462 | 1.490 | 0.310 | 0.758 | -2.576-3.501 |
| Summer | 3.702 | 1.492 | 2.481 | 0.019* | 0.658-6.746 |
| Autumn | 0.498 | 1.497 | 0.332 | 0.742 | -2.555-3.550 |

*p<0.05 was considered statistically significant

## Discussion

PUP is a serious complication of PUD, and its seasonal occurrence has been the focus of several studies. While previous research on this topic has yielded valuable insights, many studies have been limited by small sample sizes or inconsistent results due to geographical and climatic differences (8,9). Our study, based on ten years of data from a tertiary care center in Türkiye, provides a more comprehensive descriptive analysis of PUP case incidence and its seasonal fluctuations. Our findings indicate a significant seasonal imbalance in the distribution of PUP cases, with the highest incidence in summer and the lowest in winter. Notably, the peak incidence in July and the trough in September offer valuable insights into the temporal patterns of these diseases.

Seasonal variation in gastrointestinal diseases, including PUD and PUP, has been extensively reported. Some studies have suggested that colder months are associated with a higher incidence of PUD, possibly due to increased stress, dietary changes, or the exacerbation of chronic conditions (5-7). However, our findings indicate a different seasonal pattern for PUP, with a marked increase during the summer months, particularly in July. This is consistent with findings of Liu et al. (9), who observed similar trends in China, where warmer temperatures were associated with an increased incidence of PUP. This divergence between PUD and PUP serves as descriptive evidence that seasonal factors may be temporally associated with ulcer perforation, independently of PUD symptomatology. The question of why PUP often occurs in asymptomatic patients remains unanswered, and our study aimed to explore whether seasonal patterns might provide insights into these cases.

The temporal relationship driving the seasonal variation in PUP is likely multifactorial. One plausible explanation is that dietary habits during the summer months may play a significant role. Increased consumption of spicy, fatty, and acidic foods during the summer, combined with higher use of alcohol and tobacco, could exacerbate gastric irritation and increase the risk of ulcer perforation. Studies have shown that certain dietary factors, such as fatty foods, can stimulate gastric acid production, leading to mucosal damage and increased susceptibility to ulceration (10). This hypothesis aligns with our observation of a higher incidence of PUP during summer, a period traditionally associated with more frequent outdoor social gatherings, increased alcohol consumption, and greater intake of rich foods. Additionally, regional dietary habits in Türkiye during the summer months often include increased consumption of grilled meats, spicy salads, and cold, acidic beverages, which may contribute to gastric irritation.

In contrast, colder months are often linked to a higher incidence of PUD symptoms, particularly among individuals with chronic ulcer disease (6,7). However, the progression of peptic ulcer to perforation may be influenced by various factors, as reflected by the lower incidence of PUP in winter in our study. Some studies have postulated that colder temperatures may reduce gastrointestinal motility and slow gastric emptying, potentially worsening ulcer symptoms without necessarily increasing the risk of perforation (11,12). Our study supports the descriptive finding that PUP presentations are less frequent in winter, highlighting a temporal pattern that may be distinct from non-complicated PUD.

The influence of environmental factors, such as temperature and humidity, has also been proposed to contribute to the seasonal variation in PUP (9). Warmer temperatures, such as those experienced during summer in Türkiye, may be associated with dehydration and alterations in blood flow, which could reduce the protective mucus layer in the gastrointestinal tract, thereby increasing the risk of ulcer perforation. Previous studies have suggested that the incidence of ulcers, particularly duodenal ulcers, may be inversely correlated with

temperature, with lower temperatures associated with increased ulcer activity (11). However, the lack of region-specific atmospheric data in our study limits the ability to perform a comprehensive analytical correlation between climatic variations and PUP incidence. Future studies integrating detailed meteorological data are essential to establish these associations more conclusively.

The most notable finding regarding patient characteristics was the significantly younger median age (34.0 years) observed in patients presenting with PUP during the autumn months (p=0.034), a difference that warrants discussion. Although speculative given the descriptive nature of our data, this observation may suggest that a different set of factors drives perforation in younger individuals during this season. For instance, younger patients are generally less likely to have chronic *H. pylori*-driven ulcers and may have perforations that are acutely triggered by lifestyle factors. The transition from the high-stress, dietary-excess summer vacation period to the onset of the academic or work year in autumn, with September having the lowest overall incidence, may be associated with delayed presentations of ulcers or acute stress-related perforations in a younger, more reactive demographic. Alternatively, this may reflect a temporary shift in the use of NSAIDs among younger, physically active individuals as seasonal sports or activities begin. This distinct age-related pattern observed during autumn highlights the need for future analytical studies to examine the interplay of age, lifestyle, and acute triggers in PUP.

Another important factor that may contribute to seasonal patterns in PUP is the prevalence of *H. pylori* infection. Although *H. pylori* is a well-established cause of PUD, the seasonal patterns of this infection are less well understood (13). Some studies have suggested that *H. pylori* infection rates may fluctuate seasonally, with higher rates during warmer months, potentially contributing to increased PUP in summer (14). However, our study did not include data on *H. pylori* status, and further research is needed to clarify, either descriptively or analytically, the role of this infection in the seasonal distribution of PUP cases.

Additionally, the role of NSAID use in the incidence of PUP should not be overlooked. NSAIDs are known to impair the gastric mucosal defense mechanisms, making the gastrointestinal tract more vulnerable to injury. Studies have demonstrated circadian rhythms in gastrointestinal tolerance to NSAIDs, with greater susceptibility to damage occurring in the morning compared to nighttime administration (15). However, our study did not collect data on NSAID use among the study population, which constitutes a limitation to be addressed in future analytical studies.

The observed summer peak in PUP in our study is consistent with findings from other studies reporting seasonal variations in gastrointestinal conditions, particularly in warmer climates. Several factors may explain the higher incidence of PUP during the summer, including increased consumption of spicy and acidic foods, greater alcohol intake, and heightened use of NSAIDs for pain management during periods of increased outdoor activity (13). Stress levels during summer vacations and travel, coupled with disrupted dietary patterns, may temporarily exacerbate existing gastric conditions or be associated with the progression from asymptomatic ulcers to perforation. Importantly, the occurrence of PUP among non-symptomatic PUD patients suggests that acute external factors, such as those prevalent in summer months, may act as direct triggers rather than resulting from a gradual progression of ulcer severity. However, our study did not include data on these specific lifestyle factors, which limits the inferences we can draw regarding their impact on PUP incidence. Further research incorporating these variables is needed to strengthen this hypothesis.

The lower incidence of PUP observed in winter and autumn, particularly in September, could reflect changes in dietary habits and reduced NSAID use as outdoor activities decrease and stress levels potentially normalize after the summer vacation. Previous studies have suggested that lower stress and more regular dietary habits during winter months may contribute to a reduced risk of ulcer complications (16). Additionally, colder months may lack the acute triggering factors, such as dehydration or dietary excess, that are more prevalent in summer. This raises questions about the role of environmental conditions not only in ulcer formation but also in the sudden transition from ulceration to perforation. Nonetheless, these conclusions remain speculative in the absence of direct data on patient stress levels, medication use, and diet among our study population.

Additionally, our analysis did not account for variations in *H. pylori* infection rates, which could play a significant role in ulcer disease seasonality (13,14). While chronic *H. pylori* infection is well-known to contribute to PUD, the interaction between infection prevalence and acute seasonal triggers in PUP remains unclear. Higher infection rates during summer could amplify mucosal vulnerability caused by external factors, increasing the risk of perforation. Future studies should investigate the interplay between *H. pylori* status and seasonal triggers to better understand this relationship. Fluctuations in atmospheric temperature and humidity are another factor worth exploring, as several studies indicate that warmer temperatures and higher humidity may weaken gastric mucosal defenses (9,17,18). However, our study did not include region-specific meteorological data, which is a notable limitation. Future studies should incorporate detailed environmental data to better understand the climatic influences on PUP.

**Implications for Clinical Practice**

Recognizing the seasonal imbalance in PUP incidence has important clinical implications. Healthcare systems, especially in regions with clear seasonal variations, can anticipate higher demands for surgical interventions and acute care during the summer months. Hospitals could benefit from strategic planning, ensuring the availability of resources and personnel during periods of increased incidence. Furthermore, public health campaigns during high-risk months, particularly in summer, can focus on reducing risky behaviors such as excessive NSAID use and consumption of irritating foods, and on promoting adherence to ulcer prevention guidelines (16,19). By incorporating education about the potential for silent progression of ulcers to perforation, clinicians can empower patients to seek timely medical attention even in the absence of traditional ulcer symptoms. Educating patients about the signs of peptic ulcers and encouraging early medical intervention during high-incidence periods could reduce the risk of complications, such as perforation, and ultimately improve patient outcomes.

Given the high mortality associated with PUP, which is well-documented in surgical literature, it is imperative to emphasize the importance of early diagnosis and intervention. While we did not specifically report mortality rates in this study because of its retrospective design and focus on seasonal patterns, we acknowledge that mortality is a significant concern in PUP cases.

### Exploration of Additional Factors

Although this study highlights seasonal patterns in PUP, it is important to acknowledge the influence of other critical factors, such as dietary habits, stress, medication use, and *H. pylori* infection rates, which also fluctuate seasonally and can affect PUP incidence (13). In asymptomatic cases of PUD, these external factors may act as acute triggers, leading directly to perforation without warning signs. This phenomenon underscores the need for a deeper exploration of the mechanisms underlying the transition of ulcers from dormancy to perforation in response to seasonal influences. For example, studies have shown a correlation between seasonal infections and increased ulcer activity: gastrointestinal infections are often more prevalent in warmer months, which may increase the risk of ulcer perforation (14). Including data on *H. pylori* infection (a major cause of peptic ulcers) in future studies would provide valuable insights into the interaction between infection rates and PUP incidence (13,20,21). Furthermore, while natural disasters (e.g., earthquakes) and conflicts can significantly impact healthcare systems and patient stress levels, there were no major events of this nature during the study period that would have directly influenced the observed seasonal trends in our center.

### Study Limitations

Our study has several limitations inherent in its design and data collection.

First, the descriptive and retrospective nature of this single-center cohort means that we can report only the temporal distribution of PUP cases. Without a control group of non-perforated PUD patients or a population-based reference, we cannot establish causality and can only provide evidence that a seasonal pattern exists.

Second, a major limitation is the lack of detailed data on key confounding factors, including NSAID use, (*H. pylori* infection status, smoking, and alcohol consumption. Since these are primary determinants of ulcer disease, their absence prevents a deeper analytical exploration of the mechanisms driving the observed seasonal pattern, particularly why perforations occur in asymptomatic patients.

Third, we did not include detailed meteorological data on local temperature, humidity, or atmospheric pressure. This limits our ability to correlate climatic variations with the observed seasonal changes in PUP incidence (9).

Fourth, while the study spanned ten years, we did not analyze year-by-year trends, which could have revealed whether the seasonal pattern persisted or shifted over time due to changes in clinical practice or environmental factors.

Finally, the single-center design and the relatively small sample size in some seasonal subgroups may limit the generalizability and statistical power of our findings to other populations or geographic regions with different climatic conditions. We acknowledge that our focus on surgical cases precludes reporting the full incidence of non-perforated peptic ulcers or bleeding from peptic ulcers in the general population; this omission avoids potential selection bias that would result from reporting unverified data.

### Future Directions for Research

Future research should aim to address these limitations by including larger, multi-center studies that capture a broader population base and more diverse climatic conditions.

Crucially, future analytical studies must include a control group of patients with non-perforated PUD or use population-based incidence rates to distinguish overall changes in ulcer incidence from specific seasonal factors precipitating perforation.

Furthermore, integrating specific, prospectively collected data on *H. pylori* infection rates, NSAID use, dietary habits, and stress levels would provide a more comprehensive understanding of the factors influencing PUP (20,21). Detailed meteorological data should also be collected and correlated with case counts to examine the impact of environmental variables.

Moreover, analyses of annual trends could reveal how seasonal patterns are influenced by advances in medical therapies, changing environmental exposures, and shifting lifestyle behaviors. This would clarify whether the mechanisms driving seasonal PUP incidence are static or dynamic. Finally, studies examining the occurrence of PUP among non-symptomatic PUD patients could provide valuable insights into acute external triggers that bypass the usual progression of ulcer symptoms. Further studies should investigate the relationship between uncomplicated peptic ulcers and perforation rate to better understand disease progression.

## Conclusion

Our descriptive study underscores the temporal imbalance in the presentation of PUP, with a clear increase in incidence during the summer months and a lower incidence in autumn and winter.

This pattern highlights the need for public health initiatives that promote healthier lifestyle choices, including reduced NSAID use and adherence to dietary recommendations during high-risk periods such as summer. Increasing physicians' awareness of these seasonal trends in PUP can improve preparedness and patient management, particularly with respect to the significantly younger patient demographic identified in autumn.

By anticipating higher PUP incidence during summer and preparing accordingly, healthcare systems can better manage patient care and potentially reduce morbidity and mortality associated with peptic ulcers.

### Ethics

**Ethics Committee Approval:** Ethical approval for the study was obtained from the Ethics Committee of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (approval number: 2024/288, date: 05.09.2024).

**Informed Consent:** Retrospective study.

**Footnotes**

**Authorship Contributions:** Surgical and Medical Practices - İ.K., F.B., H.T., O.E.; Concept - İ.K., F.B., H.T., O.E.; Design - T.C., H.K.T., K.T.; Data Collection or Processing - İ.K., F.B., H.T., O.E.; Analysis or Interpretation A.A., T.C., H.K.T., K.T.; Literature Search - A.A., T.C., H.K.T., K.T.; Writing - İ.K., F.B., H.T., O.E., A.A., T.C., H.K.T., K.T.

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# Retrospective Analysis of Outcomes Following Expandable Titanium Cage and Iliac Graft Applications in Patients Undergoing Corpectomy for Cervical Spinal Canal Stenosis

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## ABSTRACT

**Introduction:** This study aimed to compare the clinical and radiological outcomes of iliac crest autografts and expandable titanium cages in anterior cervical column reconstruction among patients undergoing cervical corpectomy for cervical spinal stenosis.

**Methods:** A retrospective analysis of 93 patients who underwent anterior cervical corpectomy between 2016 and 2023 was conducted; 61 were treated with iliac grafts and 32 with expandable cages. Clinical efficacy was assessed using the modified Japanese Orthopaedic Association (mJOA) score, while radiological outcomes were evaluated by measuring cervical lordosis (C2-C7 Cobb angle), intervertebral height, and fusion status, three months post-surgery. Complications, operative duration, and revision surgery rates were also analysed.

**Results:** Both the iliac graft and cage groups demonstrated significant postoperative improvements in mJOA scores ($p<0.001$). The iliac graft group exhibited superior early correction of cervical kyphosis, with the Cobb angle increasing from 3.17° to 9.12° ($p<0.001$), compared with the cage group's increase from 0.99° to 5.83° ($p=0.025$). Cervical alignment remained more stable over time in the iliac graft group. Complication rates were comparable between the groups; however, graft displacement occurred more frequently in the iliac graft group. In contrast, cage malposition occasionally necessitated revision surgery.

**Conclusion:** Both iliac grafts and expandable cages are effective for anterior cervical reconstruction, yielding comparable clinical outcomes and complication rates. Iliac grafts may be better suited for achieving immediate postoperative correction and maintaining stable long-term alignment. The choice of surgical technique should take into account specific patient needs and the distinct risk profiles associated with each method.

**Keywords:** Cervical spinal canal stenosis, cervical corpectomy, iliac graft, expandable titanium cage

## Introduction

First described in the 1950s, anterior approaches to the cervical spine have gained widespread acceptance as effective methods for treating cervical spinal disorders (1). These methods provide a direct approach to anteriorly located lesions, facilitating restoration of sagittal alignment and decompression. When lesions involve multiple levels or extend posteriorly into the vertebral body, a corpectomy or vertebrectomy, including the adjacent discs, may be required. Reconstruction of the anterior column requires either an implant or a bone graft. The most suitable vertebral body replacement should provide the following advantages: anterior support resistant to axial loads, deformity correction capability, primary stability, and an extended contact surface with adjacent vertebral bodies to promote rapid fusion and prevent micromotion (2).

Until recently, autologous bone grafts were the most frequently used replacements following corpectomy. However, 20-30% of patients experience donor-site complications following iliac bone grafting. These complications include hematoma, infection, neurological injury, abdominal herniation, iliac crest fracture, and persistent pain or discomfort at the donor site (3). Elderly patients often present with insufficient iliac bone stock due to age-related decreases in bone mass (4). To eliminate the need for harvesting large structural bone and to prevent donor site complications, titanium mesh cages -rigid constructs that can be filled with autologous local bone- have been developed.

Numerous studies have demonstrated that titanium cages, particularly in patients with multilevel involvement, are safe and effective in the treatment of degenerative cervical diseases, yielding favourable long-term clinical and functional outcomes (5). However, few studies

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comparing the safety and efficacy of titanium cages have been published, despite their widespread use. Radiographic assessment of fusion is more complex when titanium cages are used. Furthermore, vertebral endplate weakness increases the need for screw fixation, which in turn raises the risk of cage subsidence. A retrospective study by Chou et al. (6) reported that titanium cages were significantly less effective than iliac bone-dependent fusion, with a fusion rate of only 45.5% one year postoperatively. However, several other studies have shown that fusion rates and clinical outcomes were comparable between patients who underwent discectomy and fusion procedures with either iliac bone grafts or titanium cages (3,7). This retrospective analysis compared the outcomes of titanium cage use and iliac crest autograft use in cervical decompression and fusion procedures. We present the clinical and radiological outcomes of 93 patients with cervical spinal stenosis who underwent cervical corpectomy followed by reconstruction using either an expandable cage or an iliac graft. Neurological and functional outcomes were evaluated in patients with cervical degenerative disc disease who were treated using the anterior approach. Clinical outcomes were evaluated using the modified Japanese Orthopaedic Association (mJOA) score, and cervical lordosis, intervertebral height, and fusion status were assessed by X-ray or magnetic resonance imaging (MRI).

## Methods

In this study, we retrospectively analysed data from 93 patients of both sexes, aged 18-90 years who were diagnosed with cervical spinal stenosis and admitted to the neurosurgery department between 2016 and 2023. The study was approved by the Tekirdağ Dr. İsmail Fehmi Cumalığlu City Hospital Clinical Research Ethics Committee (approval number: 99, date: 19.04.2024). This multicenter study was conducted in two departments (İstanbul Training and Research Hospital, Fatih Sultan Mehmet Training and Research Hospital).

Follow-up data and imaging studies of patients with cervical spinal stenosis who underwent anterior reconstruction using either iliac grafts or expandable cages were evaluated. Clinical evaluation included neurological examination and assessment of the mJOA score. mJOA scores were recorded preoperatively and three months postoperatively. Fusion and graft subsidence were evaluated radiologically using computed tomography (CT) and plain radiography. In addition, patient age, sex, Cobb angle correction at the reconstruction site, MRI signal changes, length of hospital stay, operative time, complications, spinal level of complications, treatment methods, and types of revision surgery were analysed.

### Inclusion Criteria

Patients who underwent anterior column reconstruction for cervical spinal stenosis using either an iliac graft or an expandable cage were included in the study. Indications for anterior column reconstruction included pathological fractures with greater than 50% loss of vertebral body height, severe mechanical neck pain, and resection of more than 50% of the vertebral body. Patients who did not require anterior column reconstruction were excluded from the study.

### Clinical Evaluation

Age, sex, duration of symptoms (preoperative clinical course), and initial functional status (preoperative mJOA score) were among the clinical variables examined for prognostic evaluation. Clinical outcomes and the benefits of surgical intervention were assessed using the modified mJOA scale and the postoperative functional recovery (PFR) rate (8).

### Radiologic Assessment

Radiological evaluations were performed for each patient preoperatively, immediately postoperatively (before hospital discharge), and three months after surgery. Serial radiographs of the operated segment were used to evaluate spinal stability and the state of fusion. Postoperative CT scans of the affected region were obtained to document the positions of the cage and screws and to assess the extent of spinal fusion and decompression. Kyphotic deformity was evaluated on lateral radiographs of the cervical spine using the Cobb angle. The Cobb angle was measured between the superior endplate of the upper vertebra, where the corpectomy was performed, and the inferior endplate of the lower vertebra. The kyphotic angle was measured preoperatively, immediately postoperatively, at three months, and at final follow-up (range, 13-82 months; mean, 24 months). In this study, early postoperative (three-month) radiological outcomes were analysed for all patients, whereas long-term follow-up data were available for a subset of cases and used to assess maintenance of cervical alignment and fusion stability. The height of the reconstructed segment, defined as the distance between the inferior endplate of the upper vertebra and the superior endplate of the lower vertebra, was measured on lateral radiographs. All patients underwent CT and X-ray imaging three months postoperatively to assess potential cage displacement, subsidence, stability, and fusion. Determining fusion can be challenging in the presence of anterior cervical instrumentation.

### Functional Assessment

The mJOA functional disability scale was used for preoperative and three-month postoperative assessments. The PFR rate was calculated using the formula proposed by Hirabayashi et al. (9) based on the pre- and postoperative mJOA scores.

PFR (%) = \(Postoperative mJOA - preoperative mJOA\) / \(18 - Preoperative mJOA\) × 100

### Operation Procedure

Records of 93 patients who underwent single-level (n=60) or double-level (n=33) cervical corpectomy were analysed. Corpectomy types are presented in Table 1. An anterior approach was used to perform a cervical corpectomy; in some cases, additional posterior fixation was required to achieve optimal stability. The median duration from symptom onset to surgery was 12 months (range: 1-120 months). The median operative time was 4 hours (range: 2-8 hours), and the median length of hospital stay was 3 days (range: 1-60 days).

Expandable-cage reconstruction was performed using the Alton Sapimed Onspine® cylindrical titanium mesh cage following corpectomy (n=32). Great care was taken to preserve the bony endplates as much as possible during endplate preparation following corpectomy. The superior and

inferior ends of the cage were trimmed to match the sagittal contours of the adjacent vertebral endplates. Bone chips containing demineralized bone matrix and synthetic bone allograft were placed within and around each cage, both anteriorly and laterally. In these cases, autograft material was harvested from the iliac crest and the resected vertebral body. After placement of the anterior plate, controlled distracting forces were applied to correct the kyphotic deformity.

For iliac graft harvesting (n=61), after cutting the cortical tables of the iliac crest bilaterally with an osteotome or a power saw, a cortical graft of the desired size was harvested. The graft was then carefully elevated using a broad osteotome with gentle strokes. Continuous irrigation with room-temperature saline was used to prevent thermal injury and overheating.

### Follow-up

Clinical examinations were performed preoperatively, during the early postoperative period (before discharge), and at least one year after surgery. Routine follow-up examinations were conducted every three months.

### Statistical Analysis

Comparisons between the iliac graft and cage groups were performed using independent-sample tests, depending on the distribution of the data. Normality of continuous variables was assessed using the Shapiro-Wilk test. Depending on the results of normality tests, the Student's t-test or the Mann-Whitney U test was used for continuous variables, and the chi-square test was used for categorical variables. Paired analyses were conducted using the paired t-test or the Wilcoxon signed-rank test where appropriate. Descriptive statistics were used to summarize clinical and demographic characteristics. All statistical analyses were performed using SPSS Statistics for Mac, version 29.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p<0.05$.

## Results

### Baseline and Surgery Parameters

Table 1 summarizes the clinical, radiological, and demographic characteristics of the patients. A total of 93 patients underwent anterior cervical corpectomy. Sixty-one patients underwent anterior column reconstruction using iliac grafts, and 32 underwent reconstruction with expandable cages. Representative pre- and postoperative images from both groups are shown in Figures 1 and 2.

### Clinical Efficacy Assessment

Preoperative and postoperative mJOA scores, local angulation, and C2-C7 Cobb angles are presented in Table 2. In both the iliac graft and cage groups, the change in mJOA scores from before to after surgery was significant ($p<0.001$), whereas the improvement in PFR was not statistically significant ($p=0.76$). Although the difference in PFR between the two groups was not statistically significant ($p=0.76$), both the iliac graft and cage groups demonstrated significant improvement in mJOA scores after surgery ($p<0.001$). However, no statistically significant difference in PFR was observed between the two groups ($p=0.76$). Postoperative mJOA scores improved from 13.6±2.1 to 15.8±1.7 in the iliac graft group and from 13.2±2.3 to 15.5±1.9 in the cage group, indicating overall functional recovery. Preoperative and three-month postoperative mJOA scores and the changes in local angulation are presented in Table 2.

**Table 1. Demographic parameters and pre- and postoperative surgical details in the iliac graft and cage groups**

| Variable | All patients ± SD<br>93 (%) | Iliac graft ± SD<br>61 (%) | Cage ± SD<br>32 (%) | p value |
|---|---|---|---|---|
| **Age ± SD** | 54.3±10.2 | 53.7±10.2 | 55.3±10.1 | 0.48 |
| **Male**<br>**Female** | 52 (55.9)<br>41 (44.1) | 32 (52)<br>29 (48) | 20 (62)<br>12 (38) | 0.35 |
| **Corpectomy level** | | | | |
| C4 | 10 (10.8) | 5 | 5 | |
| C5 | 21 (22.6) | 12 | 9 | |
| C6 | 28 (30.1) | 22 | 6 | |
| C7 | 1 (1.1) | 0 | 1 | 0.16 |
| C3-4 | 1 (1.1) | 0 | 1 | |
| C4-5 | 6 (6.5) | 5 | 1 | |
| C5-6 | 25 (26.9) | 17 | 8 | |
| C6-7 | 1 (1.1) | 0 | 1 | |
| **Duration of operation (hour) ± SD** | 4.0±1.1 | 3.9±1.0 | 4.2±1.1 | 0.22 |
| **Duration of hospital stay (day) ± SD** | 5.4±8.3 | 3.7±4.7 | 8.5±12.0 | **0.007** |
| **Duration of symptom** | 17.3±17.3 | 16.3±12.5 | 19.2±20.1 | 0.46 |
| **MRI signal properties** | | | | |
| Normal T1/normal T2 | 31 | 20 | 11 | 0.21 |
| Normal T1/hyperintense T2 | 53 | 40 | 13 | |
| Hyperintense T1/hyperintense T2 | 9 | 1 | 8 | |

Demographic characteristics and perioperative parameters of patients in the iliac graft and cage groups. Values are presented as mean ± SD or number (percentage) unless otherwise specified. Statistical comparisons between groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables.
SD: Standard deviation, MRI: Magnetic resonance imaging

### Comparing Radiography of Patients with Iliac Grafts and Expandable Cages

In the iliac graft group, the mean Cobb angle improved from 3.17° preoperatively to 9.12° in the early postoperative period, indicating restoration of cervical lordosis ($p<0.001$). The late postoperative Cobb angle was 3.86°, representing a statistically significant improvement compared with the preoperative value ($p=0.02$). Similarly, in the expandable-cage group, the mean Cobb angle improved from 0.99° preoperatively to 5.83° postoperatively ($p=0.025$). However, at three months postoperatively, the mean C2-C7 Cobb angle was 4.31° ($p=0.33$).

In the iliac graft group, the mean early postoperative local angulation was 10.15° (range -4° to 25°), whereas the mean late postoperative local angulation was 5.9° (range -19° to 22°) ($p=0.05$). In the cage group, the mean early postoperative local angulation was 8.04° (range -11° to 26°), and the mean late postoperative angulation was 6.50° (range -9° to 24°) ($p=0.24$).

### Complications

Fourteen patients experienced surgery-related complications. In the iliac graft group, seven patients experienced complications, including one case of esophageal rupture, two malunions, one C5 palsy, one dural tear, and two graft displacements. In the cage group, seven patients experienced complications: two C5 palsies, two cases of cage malposition, one hematoma, one malunion, and one dural tear. Two patients underwent revision surgery because of screw malposition. Comparison of complication rates between the iliac graft and cage groups using the Mann-Whitney U test revealed no statistically significant difference ($p=0.114$).

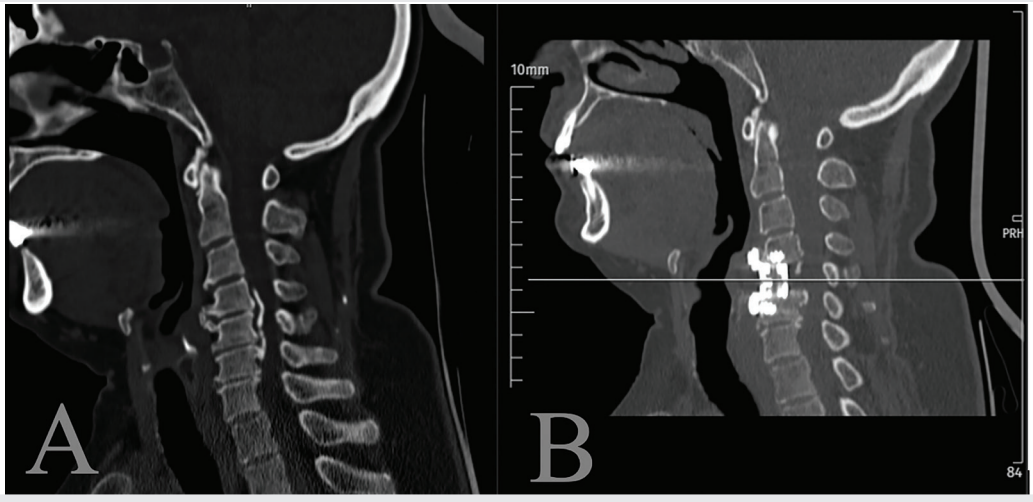


**Figure 1.** A 52-year-old male patient with C4-6 cervical spinal stenosis reconstructed with a titanium cage (preoperative mJOA score: 14). (A) Preoperative computed tomography (CT) scan showing destruction of the C4-6 posterior vertebral bodies and intervertebral discs, resulting in segmental instability. (B) Postoperative CT scan obtained 12 months after C4-6 corpectomy and titanium cage reconstruction demonstrates optimal cage positioning and satisfactory cervical stabilization (postoperative mJOA score: 17). mJOA: Modified Japanese Orthopaedic Association score

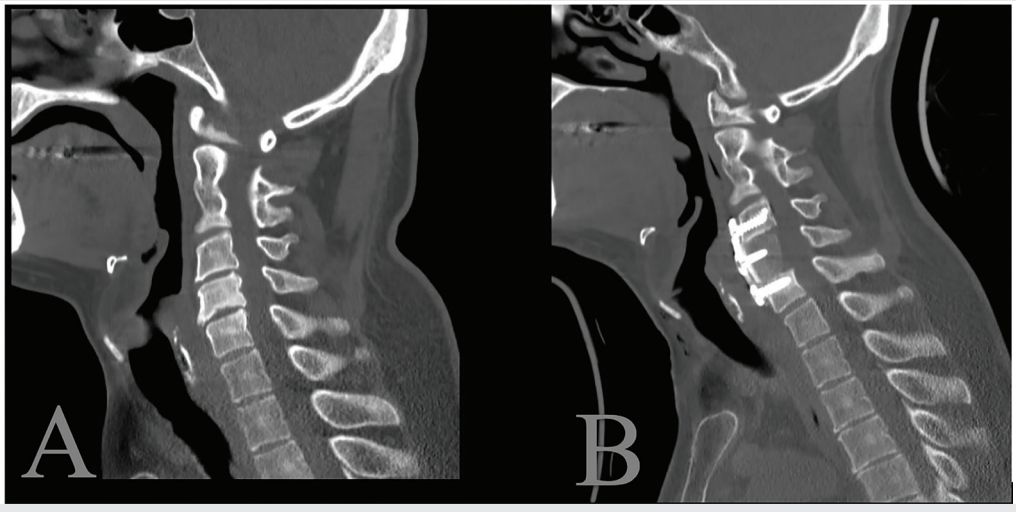


**Figure 2.** A 37-year-old male patient with C3-5 cervical spinal stenosis reconstructed using an autologous iliac graft (preoperative mJOA score: 13). (A) Preoperative computed tomography (CT) scan revealing multilevel stenosis between C3 and C5. (B) Postoperative CT scan obtained 12 months after C5 corpectomy and iliac graft reconstruction shows proper graft integration and stable cervical alignment (postoperative mJOA score: 18). mJOA: Modified Japanese Orthopaedic Association score

**Table 2. Pre- and postoperative neurological and radiological findings in the iliac graft and cage groups**

| Variable | All patients ± SD<br>93 (%) | Iliac graft ± SD<br>61 (%) | Cage ± SD<br>32 (%) | p value |
|---|---|---|---|---|
| **Preoperative C2-C7 Cobb angle** | 2.42±9.59 | 3.17±9.71 | 0.9±9.33 | 0.06 |
| **Early postoperative C2-C7 Cobb angle** | 7.99±7.66 | 9.12±7.24 | 5.83±8.08 | **0.04** |
| **Late postoperative C2-C7 Cobb angle** | 4.14±8.34 | 3.86±7.01 | 4.31±9.01 | 0.80 |
| **Early postoperative local angulation** | 9.4±7.47 | 10.1±6.55 | 8.04±8.91 | 0.19 |
| **Late postoperative local angulation** | 6.1±7.63 | 5.91±7.58 | 6.53±7.85 | 0.70 |
| **Preoperative mJOA scores**<br>Mild (mJOA >15)<br>Moderate (mJOA 12-14)<br>Severe (mJOA <12) | <br>55<br>29<br>9 | <br>35<br>23<br>3 | <br>20<br>6<br>6 | **0.04** |
| **Postoperative mJOA scores**<br>Mild (mJOA >15)<br>Moderate (mJOA 12-14)<br>Severe (mJOA <12) | <br>79<br>6<br>8 | <br>55<br>3<br>3 | <br>24<br>3<br>5 | 0.13 |

Pre- and postoperative neurological and radiological findings in the iliac graft and cage groups Values are presented as mean ± standard deviation or number (percentage) unless otherwise specified. C2-C7 Cobb angle and local angulation measurements were compared across time points to evaluate sagittal alignment correction and maintenance. SD: Standard deviation, mJOA: Modified Japanese Orthopaedic Association score, C2-C7: Cervical vertebrae 2 to 7

## Discussion

Currently, the gold standard for anterior column reconstruction following corpectomy is the use of an autologous bone graft harvested from the iliac crest. Nevertheless, approximately 25% of patients undergoing this procedure have been reported to experience donor-site complications. The most common complications include postoperative donor-site pain, hematoma or seroma formation, bone fracture, infection, and blood loss (10). Consequently, many surgeons prefer to use titanium cages to avoid these donor-site morbidities. Numerous interbody fusion devices have been developed to overcome the limitations of bone grafts, enhance endplate-to-graft apposition, and provide immediate postoperative spinal stability. These devices are made from various materials, including titanium, titanium alloys (such as titanium–aluminium–vanadium alloys), and polyetheretherketone (11). Titanium remains the principal material due to its superior corrosion resistance, biocompatibility, and high strength-to-weight ratio. Titanium promotes osseointegration, a process in which the implant directly integrates with the surrounding bone. Moreover, the surface of titanium cages can be modified to enhance cell adhesion and promote osseointegration (12). Although titanium cages are widely used, there is limited and conflicting evidence directly comparing the clinical outcomes of patients treated with expandable cages versus those treated with iliac grafts (3). The aim of this study was to compare the risks and benefits of autogenous iliac crest bone grafts and titanium cages for anterior column reconstruction in patients with cervical spinal stenosis.

### The Clinical Efficacy of Using Iliac Grafts vs. Expandable Cages

When comparing the clinical outcomes between the iliac graft and expandable-cage groups as measured by the preoperative mJOA scale and PFR rate, both groups demonstrated significant improvement in mJOA scores, whereas the difference in PFR between groups was not statistically significant. This finding suggests that iliac grafts may be used as effectively as titanium cages for anterior column reconstruction. In clinical practice, given the costs of implant manufacturing and materials, reconstruction with autologous bone grafts remains the treatment of choice.

### Cobb Angles of Cervical Curvature in Early and Late Postoperative Periods

A stable Cobb angle between the early and late postoperative periods indicates that the surgical technique provides durable correction, contributing to the long-term success of spinal fusion. Techniques demonstrating minimal regression of the Cobb angle over time indicate more robust stabilization, potentially reflecting improved bone integration, load distribution, or structural integrity (13). Analysis of the radiographic outcomes comparing iliac grafts with expandable cages showed evident postoperative improvements in cervical alignment, as measured by the Cobb angle, in both groups. Although both groups exhibited significant early postoperative improvements, a slight regression in Cobb angles was observed during the late postoperative period. In a previous comparative study of iliac grafts and titanium cages, both groups achieved solid bone fusion and all patients demonstrated marked improvement in neurological function, as reflected by increased mJOA scores (3). Tosun et al. (14) reported that expandable cages were more effective in preventing the loss of sagittal alignment. However, in a similar study, Debnath et al. (15) observed that the absence of kyphosis correction had no impact on overall neurological recovery. A minor loss of kyphotic correction or of intervertebral height is clinically acceptable.

### Local Angulation and its Role on Surgical Outcomes

Local angulation plays a significant role in determining surgical outcomes, particularly in anterior cervical column reconstruction. When postoperative local angulations were compared between the iliac graft and expandable cage groups, both groups demonstrated improvement during the early postoperative period. However, over time, partial loss of local angulation correction was observed in both groups.

This regression appeared more pronounced in the expandable-cage group. A possible explanation for this regression is that cages, typically made of titanium or other durable materials, provide immediate structural support. However, minor positional shifts may occur during integration with the surrounding bone. In addition, their use can be technically challenging, particularly when modifying the cage size to fit the defect without compromising endplate integrity.

### Complications and their Implications for Surgical Choices

Both techniques demonstrated similar complication rates, with seven complications reported in each group: in the iliac graft group, complications included one esophageal rupture, two malunions, one C5 palsy, one dural tear, and two graft displacements; in the cage group, complications included two C5 palsies, two cases of cage malposition, one hematoma, one malunion, and one dural tear. These complications pose distinct clinical risks. Malunion can impair spinal stability and healing, whereas C5 palsy may compromise upper limb function and require prolonged rehabilitation. Dural tears increase the risk of cerebrospinal fluid leakage, and displacement of the graft or cage may necessitate revision surgery. A limitation of this study is that postoperative pain at the surgical site was not assessed as a complication for the iliac graft group.

### Revision Surgery: Indications and Outcomes

In anterior cervical corpectomy for cervical stenosis, the choice between iliac grafts and expandable cages may influence the likelihood of requiring revision surgery. In our study, only two patients in the cage group required revision surgery due to implant malposition. Both patients had prolonged recovery periods (hospital stays of 14 and 10 days, respectively), yet both demonstrated improvement in their mJOA scores, reaching 17 postoperatively. To minimize the need for revision surgery and prevent implant malposition, meticulous preoperative planning using advanced imaging, together with refined surgical techniques, is essential. These revision surgeries underscore the potential risks associated with inaccuracies in implant placement.

### Study Limitations

The relatively small sample size constitutes one of the primary limitations of this study. This sample size may be insufficient to fully evaluate differences in early and late postoperative outcomes and complication rates. Additionally, because the study was retrospective, the unequal distribution of patients between the iliac graft (n=61) and cage (n=32) groups, along with the absence of a prior power analysis, may have reduced the statistical power for subgroup comparisons. Furthermore, selection bias could not be completely eliminated, as surgeon preference played a major role in determining the reconstruction method. Prospective, long-term studies with balanced group sizes are warranted to more accurately assess the comparative outcomes of iliac grafts and expandable cages.

## Conclusion

In conclusion, both expandable cages and iliac grafts effectively improve postoperative mJOA scores following anterior column reconstruction. Although expandable cages provide superior early correction of cervical kyphosis, iliac grafts offer more stable long-term alignment; therefore, the choice of reconstruction method should be individualized based on each patient's clinical and radiological characteristics. Although each technique carries distinct risks, their overall complication rates are comparable. Iliac grafts are more prone to displacement, whereas cage malposition may require revision surgery. For patients requiring immediate postoperative alignment correction, iliac grafts may represent a more favourable option; nevertheless, the approach selected should take into account the specific complication profile associated with each method.

### Ethics

**Ethics Committee Approval:** The study was approved by the Tekirdağ Dr. İsmail Fehmi Cumalığlu City Hospital Clinical Research Ethics Committee (approval number: 99, date: 19.04.2024).

**Informed Consent:** The written informed consent was obtained from all participants.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - H.D.; Concept - H.D., N.Ş.; Design - N.Ş.; Data Collection or Processing - H.D., N.Ş.; Analysis or Interpretation - H.D.; Literature Search - H.D., N.Ş.; Writing - H.D., N.Ş.

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# Strategies to Maintain A Normocalcemic, Asymptomatic Status Following Total Thyroidectomy

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## ABSTRACT

**Introduction:** Hypoparathyroidism is an unintended complication of total thyroidectomy that may result from accidental parathyroid gland excision or devascularization. However, its management remains clinically and surgically challenging. We aimed to investigate associations between postoperative hypoparathyroidism and parathyroid gland excision, vascular integrity, and early replacement therapy.

**Methods:** We retrospectively analyzed 536 patients who underwent total thyroidectomy between August 2022 and April 2025. Patients with records of preoperative and postoperative parathyroid hormone (PTH) and calcium levels , including 4- and 8-week values, were included in the study. The effects of calcium and active vitamin D replacement therapies were evaluated.

**Results:** Transient hypoparathyroidism occurred in 18.7% of patients; no cases of permanent hypoparathyroidism were detected. The mean PTH reduction rate was significantly higher in the hypoparathyroidism group (71.71%) than in the non-hypoparathyroidism group (38.44%; $p<0.05$). No statistically significant difference in PTH reduction was found between patients with and without accidental gland excision. Early calcium and active vitamin D supplementation reduced the incidence of symptomatic hypocalcemia.

**Conclusion:** Preservation of parathyroid function after thyroid surgery depends on vascular integrity and early replacement therapy with calcium and active vitamin D rather than solely on avoiding gland excision. Early biochemical monitoring and proactive supplementation could mitigate the risk of symptomatic hypocalcemia.

**Keywords:** Total thyroidectomy, hypoparathyroidism, parathyroid hormone (PTH), hypocalcemia prevention, calcium supplementation

## Introduction

Postoperative hypoparathyroidism, a common complication of thyroid surgery, results from accidental excision, devascularization, or trauma-induced functional loss of parathyroid glands. The incidences of transient and permanent hypoparathyroidism following total thyroidectomy range from 10 % to 30 % and from 1 % to 7 %, respectively (1-3). This condition significantly affects patients' quality of life and may lead to serious complications due to hypocalcemia, such as muscle spasms, paresthesia, cardiac arrhythmias, and laryngospasm (4).

Identifying the parathyroid glands *in situ* and preserving their vascular integrity are essential for maintaining parathyroid function. Lorente-Poch et al. (5) demonstrated that *in situ* preservation of parathyroid glands significantly reduced the risk of permanent hypoparathyroidism. Modern surgical tools, such as near-infrared autofluorescence (NIRAF), indocyanine green (ICG) fluorescence imaging, and carbon nanoparticles, have improved gland identification, vascular integrity, and surgical safety (6).

In this study, we retrospectively analyzed the relationship of postoperative hypoparathyroidism with accidental parathyroid gland excision and with the rate of parathyroid hormone (PTH) decline in patients who underwent total thyroidectomy for benign and malignant disease.

## Methods

Patients who underwent total thyroidectomy with or without neck dissection for thyroid cancer, follicular nodular disease, or Graves disease between August 2022 and April 2025 were included. PTH and calcium levels were analyzed preoperatively, at 1 h postoperatively, on postoperative day 1, and at weeks 4 and 8.

Patients with PTH levels ≤15 pg/mL on postoperative day 0 were classified as having early hypoparathyroidism. Those with PTH levels between 10 and 15 pg/mL received oral elemental calcium (2 × 600 mg) and calcitriol (2 × 0.5 µg) for 1 month, followed by tapering of the doses. Patients with PTH <10 pg/mL received oral calcium (600 mg three times daily)

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and calcitriol (0.5 µg three times daily), followed by one month of maintenance therapy with calcium (600 mg elemental once daily) and calcitriol (0.5 µg once daily).

Patients who underwent thyroidectomy with or without central neck dissection were hospitalized for one day, whereas those who underwent thyroidectomy with lateral neck dissection were hospitalized for three days. None of the patients required intravenous calcium replacement.

### Statistical Analysis

In this study, the mean rate of decline and the arithmetic mean of individual declines were used for statistical analyses, whereas the independent-samples t-test was used for group comparisons. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.

This was a retrospective analysis of anonymized patient data. The study was approved by the Acıbadem University Ethics Committee (approval number: 2025-12/94, date: 10.07.2025). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments.

## Results

Our cohort included 536 patients (404 women and 132 men; mean age, 44 years; range, 21-77 years). The diagnoses included papillary thyroid carcinoma (n=316), non-toxic follicular nodular disease (n=152), Graves disease (n=52), and toxic follicular nodular disease (n=16). Among the 316 patients with papillary carcinoma, 68 underwent central neck dissection and 52 underwent additional lateral neck dissection (44 unilateral and 8 bilateral; Table 1).

According to pathology reports, 88 (4.1%) of the 2,144 parathyroid glands excised from 536 patients (16.4%) were removed for the following reasons: 4 for carcinoma invasion, 8 for intrathyroidal location, and 76 due to accidental excision. None of the patients had more than one gland excised. Parathyroid glands were not autotransplanted.

In our series, the mean preoperative serum vitamin D level was 22.7 nmol/L (range 7.1-46.8 nmol/L).

Postoperative day 1 PTH levels <15 pg/mL were observed in 104 patients (18.7%), of whom 32 had glands accidentally excised (30.7%). Only 12 patients (1.5%) remained symptomatic despite the normalized PTH and calcium levels at the eighth week. This subgroup included eight patients with carcinoma who underwent neck dissection and four patients with Graves' disease.

Among patients with thyroid carcinoma, 68 had PTH levels <15 pg/mL (21.5%). Of the 1,264 parathyroid glands at risk, 64 (5%) were identified in the final pathology reports, with 28 (43.7%) showing PTH levels <15 pg/mL. Of the 32 patients with accidental gland excision and PTH levels <15 pg/mL, 20 (62.5%) underwent lateral neck dissection.

In the follicular nodular disease group, 20 of 152 patients (13.2%) had PTH levels <15 pg/mL. Twenty-four patients (3.9%) had parathyroid tissue in their pathology reports, with only four showing low PTH levels.

Among patients with Graves' disease, 12 of 52 (23.1%) had low PTH levels and had not undergone gland excision. Four of 16 patients with toxic follicular nodular disease (25%) had low PTH levels and no glands excised (Table 2).

In the eighth postoperative week, all patients had normalized PTH and calcium levels, and no cases of permanent hypoparathyroidism were identified.

Among 104 patients with hypoparathyroidism, PTH levels declined by 72.51% in patients with gland excision and by 69.66% in those without (p=0.686). In 88 patients with excised glands, PTH levels decreased by 52.17%; in 448 patients without excised glands, the decrease was 43.5% (p=0.116). The mean PTH reduction was 71.71% among 104 patients with early hypoparathyroidism. Among the remaining 432 patients, the mean PTH reduction was 38.44%, which differed significantly (p<0.05) (Tables 3-5).

None of the patients required readmission after surgical discharge.

**Table 1. Demographic and clinical characteristics of the study cohort**

| Category | Value |
|---|---|
| **Total number of patients** | 536 |
| Women | 404 |
| Men | 132 |
| **Mean age (range)** | 44 years (21-77 years) |
| **Diagnoses** | |
| Papillary thyroid carcinoma | 316 patients |
| Nontoxic follicular nodular disease | 152 patients |
| Graves disease | 52 patients |
| Toxic follicular nodular disease | 16 patients |
| **Neck dissections (among patients with carcinoma)** | |
| Central neck dissection | 68 patients |
| Lateral + central neck dissection | 52 patients (44 unilateral, 8 bilateral) |

**Table 2. Parathyroid hormone <15 pg/mL and parathyroid gland excision based on diagnosis**

| Diagnosis | n | PTH <15 pg/mL (n,%) | Parathyroid tissue in pathology (n,%) | With PTH <15 among those (n, %) | Lateral neck dissection (if excised) |
|---|---|---|---|---|---|
| **Papillary thyroid carcinoma** | 316 | 68 (21.5%) | 64/1264 glands (5%) | 28/64 (43.7%) | 20/32 (62.5%) |
| **Follicular nodular disease** | 152 | 20 (13.2%) | 24 (3.9%) | 4/24 (16.7%) | — |
| **Graves disease** | 52 | 12 (23.1%) | 0 | 0 | — |
| **Toxic follicular nodular disease** | 16 | 4 (25%) | 0 | 0 | — |

PTH: Parathyroid hormone

**Table 3. Parathyroid hormone reduction based on gland excision status**

| Patient subgroup | n | Mean ± SD PTH reduction (%) | p value | Significance |
|---|---|---|---|---|
| **Patients with hypoparathyroidism** | **104** | | | |
| With gland excision | 32 | 72.51±13.8 | 0.686 | Not significant |
| Without gland excision | 72 | 69.66±14.9 | | |
| **All patients** | **536** | | | |
| With gland excision | 88 | 52.17±10.4 | 0.116 | Not significant |
| Without gland excision | 448 | 43.50±9.7 | | |

PTH: Parathyroid hormone, SD: Standard deviation

**Table 4. Comparison of mean parathyroid hormone reduction between patient groups**

| Group | Number of patients | Mean ± SD PTH reduction (%) | Statistical significance |
|---|---|---|---|
| Early hypoparathyroidism | 104 | 71.71±12.6 | |
| Others | 432 | 38.44±8.9 | |
| **p value** | — | — | **p<0.05** |

PTH: Parathyroid hormone, SD: Standard deviation

**Table 5. Parathyroid hormone reduction based on gland excision**

| Patient group | Gland excision | n | Mean ± SD PTH reduction (%) | p value | Significance |
|---|---|---|---|---|---|
| **Patients with hypoparathyroidism** | Yes | 32 | 72.51±13.8 | 0.686 | Not significant |
| | No | 72 | 69.66±14.9 | | |
| **All patients** | Yes | 88 | 52.17±10.4 | 0.116 | Not significant |
| | No | 448 | 43.50±9.7 | | |

PTH: Parathyroid hormone, SD: Standard deviation

## Discussion

Randomized studies have shown that preserving functional circulation is as crucial as preserving anatomical integrity for maintaining parathyroid function (7,8). Furthermore, intraoperative gland identification reduces the risk of hypoparathyroidism (9). Factors such as age, Graves' disease, and lymph node dissection contribute to clinical outcomes (10,11). Our findings highlight the importance of vascular preservation and early replacement therapy.

The effectiveness of rapid PTH measurement in predicting symptomatic hypocalcemia has been emphasized in previous studies. Düren (12) demonstrated that immediate postoperative assessment of PTH levels in the post-anesthesia care unit offers a reliable and safe method for early detection of at-risk patients. These findings support the use of rapid hormone measurements to guide early supplementation decisions and prevent clinical hypocalcemia, further validating our protocol for early monitoring and intervention.

The transient hypoparathyroidism rate of 18.7% is consistent with that reported in the literature (1,2), while the permanent rate of 0% reflects surgical quality and follow-up.

Wang et al. (3) identified neck dissection in patients with malignancy as a major risk factor for permanent hypoparathyroidism. Even in benign cases, hypoparathyroidism may occur without gland excision, suggesting a key role of devascularization (5).

A decline in PTH after gland excision demonstrates the effectiveness of gland removal. However, a significant decline in PTH levels in patients who did not undergo excision indicates vascular compromise (13).

In our cohort, PTH levels declined by 71.71% from the original value in patients with PTH <15 pg/mL, whereas in patients with accidental gland excision, the decline was 52.17% ($p<0.05$), confirming that early PTH is a strong predictor.

Selberherr et al. (14) reported that the incidence of biochemical hypoparathyroidism progressively increased with the number of excised parathyroid glands: 13% with no glands excised, 21% with one gland excised, 49% with two glands excised, and 83% with three or more glands excised. In our cohort, although the rate of hypoparathyroidism among patients with gland excision (32/104, 30.7%) was lower than that among those without excision (72/104, 69.2%), the difference in mean PTH reduction between the two groups was not significant (72.51% vs. 69.66%, p=0.686). This similarity supports the notion that while accidental gland excision contributes to the risk of hypoparathyroidism, devascularization and intraoperative manipulation may play an equally crucial role. These findings collectively emphasize the importance of preserving both the anatomical integrity and the vascular supply during thyroid surgery.

In our cohort, postoperative hypoparathyroidism in patients with thyroid cancer was mainly attributed to impaired vascularization of the parathyroid glands caused by extensive dissection and/or accidental gland excision. By contrast, in cases of Graves' disease with preserved parathyroid glands and minimal surgical disruption, hypoparathyroidism may be linked to vascular insufficiency secondary to chronic autoimmunity.

Lorente-Poch et al. (15) showed that hypoparathyroidism may occur despite gland preservation, owing to devascularization and manipulation. Therefore, minimizing trauma and preserving vascular integrity are essential.

Calcium-sensing receptors (CaSRs) assist parathyroid cells in responding to calcium changes. Increased CaSR activity may suppress PTH release, thereby weakening compensation for hypocalcemia. This pathway involves both hormonal and receptor-level modulation (16,17).

Routine calcium and active vitamin D supplementation stabilizes calcium levels and supports gland recovery. Meta-analyses by Edafe et al. (19) and Ritter et al. (18) found that early replacement prevents hypocalcemia and that early PTH measurement is a strong predictor.

In our cohort, 12 patients with normalized PTH and calcium levels exhibited symptoms despite not receiving supplements. We believe that CaSR saturation may explain this discrepancy, and further studies are necessary.

Advanced imaging techniques, such as ICG angiography, allow real-time intraoperative assessment of parathyroid gland perfusion and have shown promise in reducing postoperative hypoparathyroidism. Zaidi et al. (6) reported that ICG angiography correctly predicted parathyroid viability, with a sensitivity of 97% and a specificity of 95%, and that its use was associated with a hypoparathyroidism rate as low as 5%. Similarly, other studies have shown that identifying at least one well-perfused gland using ICG may significantly reduce the risk of transient and permanent hypoparathyroidism.

In our study, ICG was not used. Instead, surgical outcomes were achieved through meticulous dissection and early replacement therapy. Even without perfusion imaging, we achieved a transient hypoparathyroidism rate of 18.7% and a permanent rate of 0%, underscoring the critical role of surgical experience and early intervention. Although ICG may be a valuable adjunct, our findings suggest that its absence does not preclude excellent outcomes when fundamental surgical principles are applied rigorously.

NIRAF enables intraoperative parathyroid identification by intrinsic tissue fluorescence at ~820 nm. Previous studies demonstrated improved gland detection and reduced postoperative hypoparathyroidism, with Falco **et al.** (20) reporting a decline in transient hypoparathyroidism from 23% to 8% under NIRAF guidance. Despite these advantages, heterogeneity among studies, equipment costs, and limited accessibility have restricted its routine use (21).

In our series, transient and permanent hypoparathyroidism rates were 18.7% and 0%, respectively; these outcomes were achieved without NIRAF or other imaging technologies. These results, which fall between conventional rates (20-30%) and NIRAF-assisted rates (as low as 8%), suggest that meticulous surgical dissection combined with early supplementation can yield outcomes comparable to technology-assisted approaches.

Our findings suggest that early replacement of calcium and active vitamin D, rather than sole reliance on visual identification, plays a crucial role in prevention. Timely physiological support allows for the recovery of gland function and prevents hypocalcemia.

Our results are consistent with the findings of Ertaş et al. (22), who reported a transient hypoparathyroidism rate of 19.2% following total thyroidectomy for benign thyroid diseases, with no cases of permanent hypoparathyroidism. Their study, which reported findings similar to those in our cohort, emphasized that meticulous surgical technique and early supplementation with calcium and vitamin D significantly reduced the incidence of symptomatic hypocalcemia. This supports the effectiveness of a proactive replacement strategy and careful tissue handling, even in the absence of advanced imaging technologies, to preserve parathyroid function and minimize complications.

**Study Limitations**

Hypoparathyroidism not only affects patients' quality of life but also imposes a substantial economic burden on healthcare systems. A comprehensive French national cohort study showed that patients who developed postoperative hypoparathyroidism incurred significantly higher medical costs in the first postoperative year than those without the condition (4). These costs were primarily driven by frequent emergency visits, repeated biochemical monitoring, prolonged medication use (e.g., calcium and active vitamin D analogs), and hospital readmissions owing to symptomatic hypocalcemia. In addition, chronic hypoparathyroidism often necessitates long-term endocrinological follow-up, placing a persistent strain on healthcare resources. From a broad perspective, this condition contributes to indirect costs, including loss of productivity, patient anxiety, and reduced work capacity. Therefore, effective prevention through meticulous surgical techniques and early biochemical support is not only clinically prudent but also economically advantageous, reducing the financial impact on both patients and health systems.

## Conclusion

Hypoparathyroidism remains a common complication of thyroid surgery. Identification and preservation of the parathyroid glands and their vascularity, and autotransplantation in cases of complete excision, are needed. Early postoperative PTH levels are useful predictors. Routine calcium and active vitamin D supplementation effectively prevents symptoms of hypoparathyroidism. Meticulous surgical planning and multidisciplinary monitoring are essential to ensure patient safety and quality of life.

### Ethics

**Ethics Committee Approval:** The study was approved by the Acıbadem University Ethics Committee (approval number: 2025-12/94, date: 10.07.2025).

**Informed Consent:** This was a retrospective analysis of anonymized patient data.

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### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - B.E., H.K., Ş.D., S.G., M.D.; Concept - B.E., M.D.; Design - B.E., M.D.; Data Collection or Processing - B.E., H.K., Ş.D., S.G.; Analysis or Interpretation - B.E., H.K., Ş.D., S.G.; Literature Search - B.E., Ş.D., S.G.; Writing - B.E., M.D.

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# Relationship Between SYNTAX Score and New Inflammatory Marker (The Aggregate Index of Systemic Inflammation) in Patients Diagnosed with Non-ST-Segment Elevation Myocardial Infarction

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## ABSTRACT

**Introduction:** Coronary artery disease is a growing global concern, and inflammation plays a significant role in its development. Inflammation is associated with plaque formation, rupture, endothelial dysfunction, platelet aggregation, and thrombus formation. Non-ST-segment elevation myocardial infarction (NSTEMI) accounts for 75% of acute coronary syndrome cases. The inflammatory response tends to increase prior to acute myocardial infarction (AMI) and becomes highly active after AMI. The Aggregate Index of Systemic Inflammation (AISI), a composite of multiple inflammatory markers, is a significant predictor of adverse outcomes in NSTEMI patients and underscores the role of inflammation in AMI. However, existing data do not indicate a correlation between the SYNTAX score (SXscore) and AISI in patients with NSTEMI.

**Methods:** This study included 226 NSTEMI patients who underwent coronary angiography between January 2022 and December 2023. The SXscore is categorized into low (≤22) and intermediate-high (>22) groups. The AISI was used to assess systemic inflammation in whole blood.

**Results:** The study included 153 participants with an SXscore ≤22 and 73 with an SXscore >22. Laboratory analysis indicated significantly higher AISI levels in the cohort with an SXscore >22 (p=0.027). Multivariable logistic regression showed that age (p=0.010) and AISI levels (p=0.017) independently predicted the intermediate-high SXscore and the group with SXscore >22, respectively.

**Conclusion:** The AISI, a biomarker, can identify patients with intermediate-to-high SXscore, aiding early risk assessment and triage decisions. Patients with high values require aggressive treatment.

**Keywords:** Non-ST-segment elevation myocardial infarction, the Aggregate Index of Systemic Inflammation, SYNTAX score

## Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide, and its prevalence is steadily rising, making it an increasingly common cardiovascular condition (1,2). Although atherosclerotic plaques in the coronary arteries are primarily linked to lipid accumulation (1), recent studies highlight the importance of inflammation, as evidenced by markers such as the systemic immune-inflammation index (SII) and the neutrophil-lymphocyte ratio (NLR). This study underscores the central role of inflammation in the initiation and progression of CAD (3-5). Inflammatory responses are deeply linked not only to plaque formation but also to endothelial dysfunction and thrombus formation (6). Non-ST-segment elevation myocardial infarction (NSTEMI) is a form of acute coronary syndrome (ACS), representing about 75% of ACS cases (1).

Despite medical advances, ACS remains a leading cause of illness and death worldwide. An inflammatory response begins before the onset of acute myocardial infarction (AMI) and becomes excessively active afterward. This highlights, to some extent, the inflammatory aspect of the condition (7). Early detection of high-risk individuals in this patient group is essential to improve prognosis. Recent efforts have focused on identifying new markers to better distinguish high-risk patients. Numerous scientific studies have demonstrated that inflammatory processes influence the mechanisms involved in the development and complications of atherosclerotic plaques, ultimately contributing to the onset of ACS. Consequently, novel indices, such as the Aggregate Index of Systemic Inflammation (AISI), SII, and the Systemic Inflammatory Response Index, have been developed to quantify the equilibrium between systemic inflammation and the immune response and to serve

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as objective markers (8). There is a broad consensus that composite inflammation indices, which integrate multiple markers, offer a more comprehensive perspective on inflammation than single indicators.

In this context, AISI was introduced in 2018 (9). Many NSTEMI patients have multivessel disease, and the SYNTAX score (SXscore) is crucial in selecting the optimal revascularization strategy (10).

Currently, no data demonstrate a link between AISI and CAD severity in NSTEMI patients. It is hypothesized that in these patients AISI correlates with more advanced stages of CAD, as reflected by the SXscore.

## Methods

### Study Population

This retrospective study calculated the minimum sample size required to detect an effect size of 0.2 with 90% statistical power. The sample size of the study, n=226, corresponds to the number of consecutively enrolled patients diagnosed with NSTEMI according to the European Society of Cardiology (ESC) Guidelines (11) who provided informed consent and underwent coronary angiography between January 2022 and December 2023. Specifically, the SYNTAX ≤22 group had a mean age of 62.4±10.2 years and 69.9% were male, while the SYNTAX >22 group had a mean age of 66.6±12.2 years and 72.6% were male. The Non-Interventional Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University approved the study (approval number: 2025/14, date: 09.07.2025), and the study was conducted in accordance with the Declaration of Helsinki. Patients were excluded if they had conditions that could influence systemic inflammatory markers, including chronic inflammatory or autoimmune diseases; active infection or sepsis; hematologic disorders (such as anemia or leukopenia); active or prior malignancy; severe renal dysfunction; liver dysfunction; recent major surgery or trauma; recent vaccination (within one month); recent blood transfusion or antibiotic use (within three months); glucocorticoid therapy (within two months); myocardial infarction with non-obstructive coronary arteries; or missing laboratory data. Figure 1 presents the flowchart of the study's exclusion criteria.

### Clinical and Laboratory Data

The patient demographic data, as well as the clinical, laboratory, and angiographic data, were retrieved from the institutional database.

The NSTEMI diagnosis was made according to the ESC guidelines for the treatment of ACS. For this diagnosis, at least one of the following criteria must be present, particularly when accompanied by elevated troponin

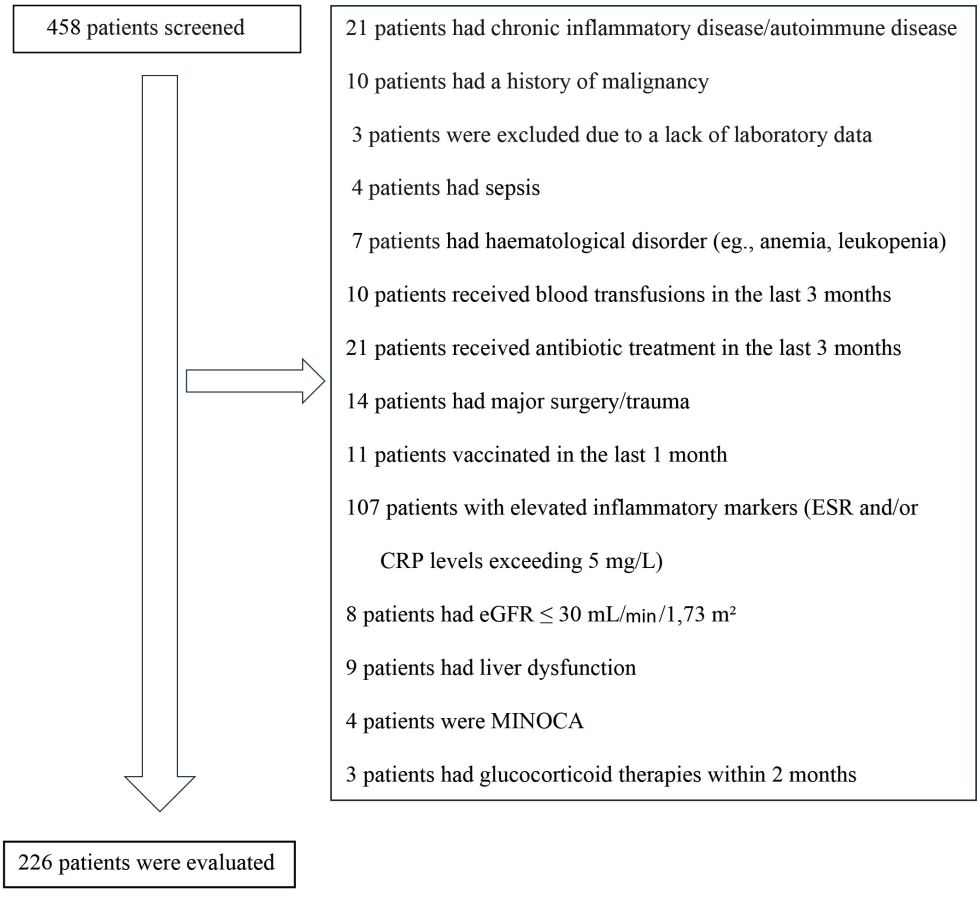


**Figure 1.** The exclusion criteria for the study population
ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, MINOCA: Myocardial infarction with non-obstructive coronary arteries

levels: symptoms suggestive of ischemia, particularly of recent onset, presence of pathological Q waves on electrocardiogram, evidence of new loss of viable myocardium on imaging studies, detection of segmental abnormalities in cardiac wall motion, or detection of coronary artery thrombus during angiography (11).

Smokers are people who have been smoking regularly for the past six months. Hypertension (HT) is defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg, or a prior diagnosis of HT requiring treatment (12). Diabetes mellitus (DM) was defined as a fasting plasma glucose level ≥126 mg/dL or the use of antidiabetic medication in individuals with a history of DM (13). Hyperlipidemia is characterized by a total cholesterol level exceeding 200 mg/dL, a low-density lipoprotein cholesterol level exceeding 130 mg/dL, or a documented history of hypercholesterolemia that was diagnosed and managed (14). Peripheral arterial disease is characterized by occlusion of one or more peripheral arteries, typically due to atherosclerosis, thrombosis, embolism, scoliosis, or fibromuscular dysplasia (15).

All metabolic and basic blood parameters were evaluated, and a complete blood count was measured in peripheral venous blood samples obtained at the time of NSTEMI diagnosis. The lipid panel and fasting plasma glucose levels were determined from the first blood samples obtained after at least 12 hours of fasting during hospitalization. Laboratory parameters, including routine blood tests, were analyzed at our hospital.

AISI was determined by multiplying the neutrophil, platelet, and monocyte counts and dividing the product by the lymphocyte count, using laboratory data (9).

### Assessment of Coronary Angiography and Calculation of SYNTAX Score

Patients diagnosed with NSTEMI underwent coronary angiography, performed by experienced interventional cardiologists using the Seldinger technique, within the first 24 hours of hospital admission, and the angiographic results were evaluated. Images of the left anterior descending, left circumflex, and right coronary arteries were assessed from various angiographic angles.

Decisions on revascularization strategies and medical follow-up were left to physicians' discretion. When percutaneous coronary intervention (PCI) was indicated, it was performed using conventional techniques during the same session. Before angiography, all patients received a 300 mg loading dose of acetylsalicylic acid, a P2Y12 inhibitor, and a standard dose of unfractionated heparin (50-70 U/kg).

An independent cardiologist, unaware of the patients' clinical characteristics, determined the SXscore. The SXscore was used to assess the anatomical severity of coronary narrowing, focusing on coronary vessels with diameters exceeding 1.5 mm and on segments with over 50% narrowing (http://www.SYNTAXscore.com) (16,17). The variability within observers in defining the SXscore was 1%, while the variability between observers was 2%. In our study, the SXscore was categorized into two groups-low (≤22) and intermediate-high (>22)- and subsequently analyzed.

### Statistical Analysis

Statistical analyses were conducted using SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables are expressed as percentages, and continuous variables are shown as mean ± standard deviation. The independent samples t-test or the Mann-Whitney U test, as appropriate, was used to analyze continuous variables, and the $\chi^2$ test was applied to categorical variables. Variables with significant univariable regression coefficients for an intermediate-to-high SXscore were included in a multivariable regression analysis to identify independent predictors of an intermediate-to-high SXscore. Receiver operating characteristic (ROC) analysis was used to determine the cut-off levels of AISI for predicting an intermediate-to-high SXscore. The statistical significance level was set at $p<0.05$, and 95% confidence intervals (CIs) were calculated.

## Results

### Baseline Characteristics

All study participants were included: 153 (67.70%) had SXscore ≤22 and 73 (32.30%) had SXscore >22. No statistically significant differences were observed between the two groups with respect to sex, body mass index (BMI), comorbidities, or laboratory values (all $p>0.05$). However, the prevalence of DM was higher in the SXscore >22 group than in the SXscore ≤22 group [47 (64.3%) vs. 72 (47.1%); $p=0.037$]. Similarly, the mean age was higher in the SXscore >22 group (66.6±12.2 years vs. 62.4±10.2 years, $p=0.020$). Patients with a SXscore >22 had significantly higher AISI values than those with a SXscore ≤22 (482.9±233.8 vs. 416.0±198.6; $p=0.027$) (Table 1).

### Predictors of SYNTAX Score >22 Group

Multivariable logistic regression analysis was conducted to identify independent predictors of SXscore in NSTEMI patients. Logistic regression analysis identified age ($p=0.010$) as an independent predictor of an intermediate-high SXscore. Additionally, AISI levels were found to be independent predictors of membership in the SXscore >22 group [odds ratio (OR): 1.002; 95% CI: 1.000-1.003; $p=0.017$]. In the multifaceted model, The probability ratio for AISI indicated that each one-unit increase in AISI was associated with a greater probability of an intermediate-to-high SXscore. This finding supports the independent prognostic value of AISI beyond traditional cardiovascular risk factors and established inflammatory markers (Table 2).

### ROC Analysis for AISI

ROC curve analysis was performed to evaluate AISI's ability to predict which patients have an SXscore >22. The study demonstrated that AISI had significant discriminative ability, with an area under the curve (AUC) that indicated good predictive performance in identifying complex coronary anatomy in NSTEMI patients. The AUC of the AISI for predicting the occurrence of the SXscore in patients was 0.578 (95% CI: 0.497–0.659; $p=0.047$). The cut-off value of the AISI for predicting the SXscore was 398.6, with sensitivity and specificity of 0.534 and 0.536, respectively (Figure 2).

**Table 1. Demographic features and laboratory findings of patients by SYNTAX score groups**

| Variables | SYNTAX score ≤22 (n=153) | SYNTAX score >22 (n=73) | p value |
|---|---|---|---|
| Age, years | 62.4±10.2 | 66.6±12.2 | 0.020 |
| Male, gender | 107 (69.9) | 53 (72.6) | 0.690 |
| BMI (kg/m$^2$) | 29.30±3.36 | 29.36±3.41 | 0.902 |
| Systolic BP (mmHg) | 135±16.9 | 133±15.9 | 0.377 |
| Diastolic BP (mmHg) | 79.4±10.9 | 79.2±9.3 | 0.844 |
| Previous history | | | |
| Smoking | 89 (58.2) | 35 (47.9) | 0.149 |
| Hypertension | 100 (65.4) | 48 (65.8) | 0.954 |
| Diabetes mellitus | 72 (47.1) | 47 (64.3) | **0.037** |
| Hyperlipidemia | 74 (48.4) | 37 (50.6) | 0.744 |
| PAD | 27 (17.6) | 11 (15.1) | 0.628 |
| Laboratory values | | | |
| White blood cell count (10$^9$/L) | 9.0±2.5 | 8.8±2.3 | 0.591 |
| Hemoglobin (g/L) | 13.5±1.9 | 13.2±1.5 | 0.176 |
| Creatinine (mg/dL) | 0.90±0.20 | 0.95±0.24 | 0.130 |
| LDL-C (mg/dL) | 117.8±40.9 | 116.6±40.1 | 0.816 |
| HDL-C (mg/dL) | 40.3±10.8 | 38.7±9.7 | 0.202 |
| Total cholesterol (mg/dL) | 191.4±50.2 | 186.4±43.9 | 0.401 |
| Triglyceride (mg/dL) | 167.2±90.1 | 163.7±90.9 | 0.789 |
| Glucose (mg/dL) | 140.3±66.2 | 151.3±70.0 | 0.297 |
| AISI | 416±198.6 | 482.9±233.8 | **0.027** |

Data presented as mean ± standard deviation or number (%). BMI: Body mass index, BP: Blood pressure, PAD: Peripheral arterial disease, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, AISI: Aggregate Index of Systemic Inflammation

**Table 2. Univariate and multivariate logistic regression analysis identifying the independent predictors of the presence of a SYNTAX score ≤22**

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Diabetes mellitus | 1.156 (0.542-2.020) | 0.618 | | |
| Age | 1.032 (1.008-1.056) | **0.016** | 1.035 (1.008-1.066) | **0.010** |
| AISI | 1.001 (1.000-1.003) | **0.028** | 1.002 (1.000-1.003) | **0.017** |

OR: Odds ratio, CI: Confidence interval, AISI: Aggregate Index of Systemic Inflammation

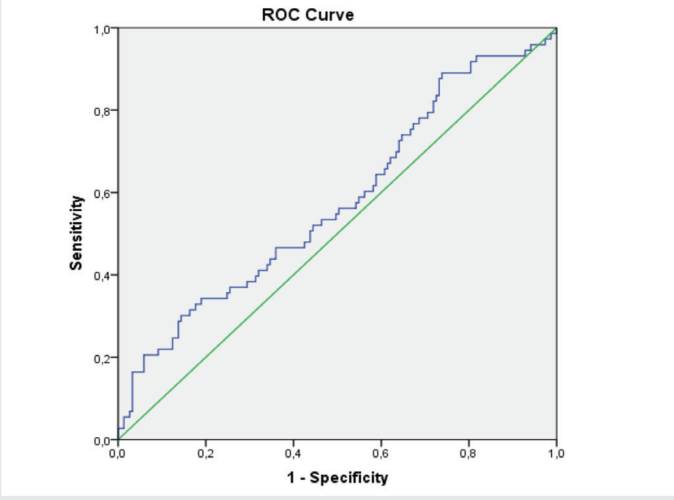


**Figure 2.** ROC curve for AISI value as a predictor of SYNTAX score >22
ROC: Receiver operating characteristic, AISI: Aggregate Index of Systemic Inflammation

## Discussion

In our cohort, patients with NSTEMI were divided into two groups based on their SXscore: those with scores >22 were considered high-risk according to clinical guidelines (16). Patients with medium-high SXscore had high AISI values, suggesting a possible link between systemic inflammation and CAD complexity. This finding is consistent with previous studies suggesting that systemic inflammation plays a significant role in the initiation, progression, and destabilisation of atherosclerotic plaques, which can lead to ACS (18). AISI has demonstrated clinically meaningful sensitivity and specificity for predicting moderate-to-high SXscore, highlighting its potential as a screening tool in clinical practice. Methods for assessing NSTEMI risk include clinical and angiographic data, as well as cardiac biomarkers. NSTEMI is associated with complex mechanisms involving systemic and local inflammatory processes that contribute to the progression of atherosclerosis and increase the risk of complications by triggering acute coronary thrombosis (19). Risk assessment tools such as Myocardial Infarction Triage and Intervention and Global Registry of Acute Coronary Events do not include inflammatory markers (20).

Current evidence suggests that inflammatory indices may enhance the prognostic value of these validated risk scores (21). In recent years, interest in inflammation and related markers has increased significantly, making it a fundamental topic in the field (22). Several studies emphasize the significance of inflammatory markers and indicators such as NLR and SII, highlighting the vital role of inflammation in the progression of CAD (23-25). The newly developed combined index, AISI, is a measure of systemic inflammation that evaluates neutrophils, lymphocytes, monocytes, and platelets (21). In patients presenting with ACS or AISI, and in those undergoing PCI, these factors have also been recognized as independent predictors of adverse clinical outcomes (23). Jiang et al. (19) have shown that elevated AISI levels in AMI patients are strongly associated with higher risks of major adverse cardiovascular and cerebrovascular events, including all-cause mortality. The study involving more than 1,044 patients showed that those in the highest AISI quartile had a 4.64-fold higher risk of all-cause mortality than those in the lowest quartile (10). Wang et al. (26) examined the link between AISI and the slow coronary flow phenomenon (SCFP) in patients with ischemia but no obstructive CAD. They found that AISI independently predicts SCFP; an optimal cut-off of 264.1 yielded sensitivity and specificity of 64.4% each. This study demonstrates the effectiveness of AISI in detecting coronary microvascular dysfunction in patients, which may represent an early stage of CAD (26). AISI offers various advantages as an additional risk classification tool. It can be obtained from standard complete blood count parameters, which are readily available in most clinical settings and do not incur additional costs or require specialized equipment. It can be detected immediately upon hospital admission, facilitating early risk assessment and triage decisions. The combined structure of AISI provides a more comprehensive assessment of inflammatory status than do individual blood cell counts or traditional inflammatory markers. The SXscore is an essential tool for evaluating coronary anatomical complexity, guiding treatment decisions, and directing revascularization strategies, but it requires invasive coronary angiography (11). The relationship between inflammatory markers and the SXscore was also examined using other composite indices. Cetinkaya et al. (21) examined the association between the pan-immuno-inflammatory value (PIV) and the severity of CAD in patients with NSTEMI. Their findings indicated that a high PIV independently predicted a higher SXscore (OR: 1.003) and correlated strongly with it (r: 0.68). Although PIV shows promise, the AISI might be advantageous because of its ease of calculation and broader applicability across different cardiovascular conditions (21). Konuş et al. (27) evaluated the advanced lung cancer inflammation index (ALI) in patients with NSTEMI and its relationship with the SXscore. Interestingly, they found an inverse relationship: lower ALI values are associated with higher SXscore. The ALI calculation incorporates the neutrophil-to-lymphocyte ratio, BMI, and serum albumin, which may explain its differing relationship with AISI (27). This underscores the importance of understanding how inflammatory indices are constructed and calculated when evaluating their clinical relevance. Specifically, inflammatory pathways are triggered by neutrophils, monocytes, platelets, and the key cytokines they produce. Additionally, circulating lymphocytes are believed to participate in certain inflammatory pathways.

The findings indicate that patients with more extensive and complex coronary atherosclerosis experience higher systemic inflammatory activation, which can accelerate disease progression and increase the risk of adverse events. AISI encompasses various cellular components of the inflammatory process and provides a more comprehensive assessment of inflammatory burden than individual biomarkers. The development of integrated risk assessment tools that combine clinical variables, traditional biomarkers, and new inflammatory indices, such as AISI, may enable more precise risk stratification and personalized treatment strategies. These tools can help identify patients who are most likely to benefit from aggressive medical treatment, early invasive procedures, or specific interventions. The AISI has been recognized as a promising biomarker for assessing CAD complexity in NSTEMI patients. Its strong correlation with the SXscore, together with its accessibility and cost-effectiveness, supports its potential for use in clinical settings. As our understanding of the inflammatory basis of CAD advances, biomarkers like AISI may become increasingly critical to personalized cardiovascular medicine and to improving patient outcomes.

Our results support recent studies showing a relationship between inflammatory markers and CAD severity. An advantage of this study is that the use of routine laboratory parameters to calculate the AISI enhances the clinical relevance of our results.

### Study Limitations

The study's cross-sectional design prevents us from establishing a causal relationship between AISI and SXscore. Prospective studies are necessary to determine whether high AISI values indicate the development of complex coronary anatomy prior to, or as a consequence of, advanced atherosclerotic disease. In this study, the AISI parameters were not measured again, and the calculations were not redone. Our population might not include all NSTEMI patients, so validation in different cohorts is necessary to determine widely applicable cut-off values. The optimal cut-off for AISI may differ depending on population characteristics (age, gender, and ethnicity) and clinical context, including comorbidity levels. Although AISI's SXscore classification shows good predictive ability, its practical use ultimately relies on how well it predicts meaningful clinical outcomes. Future research should examine whether risk classification using AISI guidance leads to better patient outcomes, such as lower mortality rates, fewer recurrent cardiovascular events, and more efficient use of resources.

## Conclusion

AISI, an advanced biomarker, has shown significant clinical potential for identifying patients with intermediate- to high SXscore. It can be calculated from routine blood count parameters at hospital admission, enabling early risk assessment and triage decisions without incurring additional costs or requiring specialized tests. Patients with high AISI values may benefit from aggressive medical treatment, closer monitoring, and potentially earlier invasive procedures. Conversely, those with lower AISI values may be suitable for conservative treatment. Identifying high-risk inflammatory phenotypes may enable personalized treatment strategies targeting both atherothrombotic and inflammatory factors

of CAD. AISI can also evaluate the effectiveness of anti-inflammatory therapy in patients. However, further validation is needed through prospective studies. Artificial intelligence methods can help create more comprehensive risk assessment tools.

### Ethics

**Ethics Committee Approval:** The Non-Interventional Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University approved the study (approval number: 2025/14, date: 09.07.2025).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Concept - N.E.G., İ.E.; Design - N.E.G., İ.E., U.K.; Data Collection or Processing - N.E.G., M.B.K., U.K.; Analysis or Interpretation - İ.E., M.B.K., U.K.; Literature Search - N.E.G., M.B.K., U.K.; Writing - N.E.G., M.B.K., U.K.

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

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# The Effect of Social Media and Internet Use on Patients Using Over-the-Counter Vitamin Supplements

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## ABSTRACT

**Introduction:** Social media and internet platforms have transformed access to health information, often encouraging the unsupervised use of over-the-counter (OTC) vitamin supplements. This trend raises concerns about the reliability of online health content and its influence on health behaviors. This study aimed to evaluate the role of social media and internet use in patients' decisions regarding OTC vitamin supplementation.

**Methods:** A cross-sectional survey was conducted among 216 patients attending an internal medicine outpatient clinic. Participants were grouped into two categories: those who independently initiated supplementation and those who were influenced by social media. Demographics, health information sources, social media habits, and supplementation practices were recorded. Serum 25-hydroxyvitamin D and vitamin B12 levels were measured, with deficiencies defined as <20 ng/mL and <200 pg/mL, respectively. Statistical analyses were performed using SPSS version 25.0, with significance set at $p<0.05$.

**Results:** Among the participants, 55.1% were male and 44.9% were female, with a mean age of 40.8±11.4 years. Social media influenced 37.5% (n=81) of participants to initiate supplementation, most commonly via Instagram (33.3% of those influenced). This group was younger (40.3 vs. 41.4 years; $p=0.001$), had higher educational attainment (95.1% vs. 76.3% university graduates; $p<0.001$), and reported greater daily social media use (>3 h: 76.5% vs. 54.8%; $p=0.006$). While no significant difference was found in vitamin D levels ($p>0.05$), the social media group had higher vitamin B12 levels (median, 358 vs. 308 pg/mL; $p=0.006$) and a lower prevalence of deficiency (1.2% vs. 8.9%; $p=0.022$).

**Conclusion:** Social media significantly influences public health behaviors, particularly by promoting OTC vitamin use. Although some users may experience benefits, unsupervised supplementation poses risks. Physician guidance and stricter regulation of online health content and influencer marketing are essential to safeguard public health.

**Keywords:** Vitamin B12, vitamin D, social media, public health

## Introduction

Social media are widely used interactive platforms where individuals search for, use, and create online content. Over the past two decades, it has become an integral part of daily life, displacing traditional media such as television, radio, and newspapers as the primary sources of information (1). Through real-time updates and personalized content, it has also transformed how individuals access health-related information.

In healthcare, social media platforms, blogs, and media-sharing sites provide valuable tools for disseminating knowledge and promoting disease prevention. However, outdated or inaccurate information may lead to misleading health decisions (2,3). Although these platforms enable healthcare professionals to reach large audiences, concerns about content reliability persist.

Approximately 75% of Internet users currently seek health information through social media and search engines, forming virtual communities to share experiences and advice (4). The parallel growth of e-commerce has facilitated the unregulated use of OTC products, dietary supplements, and vitamin complexes, often marketed as safe and effective, but consumed without medical supervision, posing public health risks (5).

Social media influencers further promote unsupervised use of supplements among adolescents and young adults. A 2021 analysis found that only 4% of medical posts on Instagram originated from

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verified accounts and that only 1% displayed a Supplement Facts label (6), emphasizing the need to ensure the reliability of online health information.

Therefore, this research aimed to investigate the impact of social media and internet use on patients who take over-the-counter (OTC) vitamin supplements.

## Methods

Patient selection and data collection:

A total of 216 subjects who were using OTC vitamin supplements and who were visiting the internal medicine outpatient clinic were included in the study after meeting the inclusion and exclusion criteria.

Inclusion criteria:

1) Patients who visited the internal medicine clinic between September 15 and September 30, 2025, and used OTC vitamin supplements.

2) Being 18-65 years of age.

3) Giving consent to participate in the study and complete the survey form.

Exclusion criteria:

1) Being <18 years or >65 years.

2) Having history of skin, liver, kidney, stomach, pancreas, or intestinal diseases.

3) Having history of using medications that inhibit the absorption of vitamin D or B12 levels.

4) Pregnancy or lactation.

5) History of gastrointestinal surgery or malabsorption syndromes.

6) Active malignancy or chronic inflammatory diseases.

7) Cognitive impairment or inability to complete the questionnaire.

The exclusion of individuals with chronic or inflammatory diseases was intended to reduce potential confounding effects on vitamin metabolism, absorption, and serum levels. This approach allowed for a more homogeneous study population and enabled a clearer interpretation of the relationship between OTC supplement use and measured vitamin concentrations.

After obtaining informed consent, a survey was conducted to collect information on each patient's age, gender, educational level, marital status, living situation (alone or with family), employment status, physical activity habits, duration of social media use, the source of the recommendation to start vitamin supplementation, the source of the most recent medical information accessed via social media, whether they experienced an improvement in well-being after taking the supplements, any side effects from the supplements, and the duration of supplement use. Additionally, blood levels of 25-hydroxy vitamin D and vitamin B12 were measured, and social media platforms used by each patient were recorded.

The cut-off value for 25-(OH)D vitamin deficiency was determined to be 20 ng/mL (7), while the cut-off for vitamin B12 deficiency was set at 200 pg/mL (8).

Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (approval number: 234, date: 12.09.2025). The research was conducted in accordance with the principles of the Declaration of Helsinki. The informed consent was obtained through institutional procedures, and all patient data were anonymized prior to analysis.

### Statistical Analysis

The normality of numerical variables' distributions was assessed using the Shapiro-Wilk test, Q-Q plots, and histograms. Comparisons of non-normally distributed variables between two independent groups were performed using the Mann-Whitney U test. The relationships between categorical variables were analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate. Descriptive statistics for non-normally distributed variables were presented as median (minimum-maximum), while categorical variables were summarized as frequencies and percentages. Statistical analyses were conducted using the SPSS software package, version 25.0 (IBM Corporation, Armonk, New York, USA). Hypotheses were tested using two-sided tests, and $p<0.05$ was considered statistically significant.

An a priori sample-size calculation (two-sided test; $\alpha$: 0.05; power: 0.80; Cohen's d: 0.46) indicated that 75 participants per group (n=75) were required. Because our study included 81 and 135 participants in the two groups, respectively, a post-hoc power analysis ($\alpha$: 0.05, d: 0.46) yielded an observed power of 0.90, confirming adequate power to detect the specified effect.

## Results

A total of 216 individuals were included in the study, of whom 55.1% were male and 44.9% were female. The mean age of the whole group was 40.82±11.44 years. Participants were divided into two groups based on their decision-making process regarding vitamin supplementation: those who made decisions independently and those who were influenced by social media. The mean age of patients who initiated vitamin supplementation on their own was 41.35±11.13 years, whereas the mean age of those who started supplementation after being influenced by social media was 40.29±11.77 years. The demographic and other characteristics of the two groups are summarized in Table 1.

Regarding education level, the majority of participants (83.3%) held a university degree or higher. The proportion of participants with a bachelor's degree or higher was significantly greater in the social media-influenced group (95.1%) than in the independent group (76.3%; $p<0.001$) (Table 1).

There were statistically significant differences between the groups regarding social media usage duration and employment rates ($p<0.05$). Among participants influenced by social media, 76.5% reported using social media for ≥3 hours, and 82.7% were employed; both proportions were significantly higher than in the independent group ($p=0.006$ and $p=0.013$, respectively) (Table 1).

**Table 1. Comparison of characteristics between cases using over-the-counter vitamin complexes influenced by social media and those using on their own initiative**

| | Use of vitamin supplementation | | | |
|---|---|---|---|---|
| | Self-initiated use (n=135) | Use influenced by social media (n=81) | Total (n=216) | |
| | n (%) | n (%) | n (%) | p |
| **Gender** | | | | |
| Male | 79 (58.5) | 40 (49.4) | 119 (55.1) | 0.191* |
| Female | 56 (41.5) | 41 (50.6) | 97 (44.9) | |
| Mean age ± SD | 41.35±11.13 | 40.29±11.77 | 40.82±11.44 | **0.001**⁺ |
| **Educational level** | | | | |
| High school or lower | 32 (23.7) | 4 (4.9) | 36 (16.7) | **<0.001*** |
| University degree or higher | 103 (76.3) | 77 (95.1) | 180 (83.3) | |
| **Duration of social media use** | | | | |
| Less than 1 hour | 26 (19.3) | 7 (8.6) | 33 (15.3) | **0.006*** |
| 1-3 hours | 35 (25.9) | 12 (14.8) | 47 (21.8) | |
| 3 hours or more | 74 (54.8) | 62 (76.5) | 136 (63) | |
| **Marital status** | | | | |
| Single | 66 (48.9) | 48 (59.3) | 114 (52.8) | 0.139* |
| Married | 69 (51.1) | 33 (40.7) | 102 (47.2) | |
| **Living arrangement** | | | | |
| Alone | 53 (39.3) | 32 (39.5) | 85 (39.4) | 0.971* |
| With family | 82 (60.7) | 49 (60.5) | 131 (60.6) | |
| **Active sports status** | | | | |
| Active | 44 (32.6) | 36 (44.4) | 80 (37) | 0.081* |
| Inactive | 91 (67.4) | 45 (55.6) | 136 (63) | |
| **Employment status** | | | | |
| Unemployed | 29 (21.5) | 10 (12.3) | 39 (18.1) | **0.013*** |
| Employed | 87 (64.4) | 67 (82.7) | 154 (71.3) | |
| Retired | 19 (14.1) | 4 (4.9) | 23 (10.6) | |
| **Where did you last obtain medical information on social media?** | | | | |
| Medical doctor accounts/websites | 52 (38.5) | 26 (32.1) | 78 (36.1) | **<0.001*** |
| Social media influencers (non-medical) | 22 (16.3) | 42 (51.9) | 64 (29.6) | |
| Social media platforms patients are subscribed to | 53 (39.3) | 7 (8.6) | 60 (27.8) | |
| Pharmaceutical company websites/pages | 8 (5.9) | 6 (7.4) | 14 (6.5) | |
| **Did you experience an improvement in overall well-being after using vitamin supplements?** | | | | |
| Yes | 74 (54.8) | 54 (66.7) | 128 (59.3) | 0.086* |
| No | 61 (45.2) | 27 (33.3) | 88 (40.7) | |
| **Have you experienced any side effects from the vitamin complexes you started without consulting your doctor?** | | | | |
| Yes | 2 (1.5) | 2 (2.5) | 4 (1.9) | 0.602* |
| No | 133 (98.5) | 79 (97.5) | 212 (98.1) | |
| **How long have you been using vitamin supplements?** | | | | |
| Less than 1 month | 36 (26.7) | 20 (24.7) | 56 (25.9) | 0.524* |
| 1-3 months | 59 (43.7) | 31 (38.3) | 90 (41.7) | |
| More than 3 months | 40 (29.6) | 30 (37) | 70 (32.4) | |
| **Vitamin B-12 level** | | | | |
| Low | 12 (8.9) | 1 (1.2) | 13 (6) | **0.022*** |
| Normal | 123 (91.1) | 80 (98.8) | 203 (94) | |
| Mean vitamin B12 level ± SD | 333.31±116.02 | 343.93±92.21 | 338.62±104.68 | **0.006**⁺ |
| **25-hydroxy vitamin D level** | | | | |
| Low | 34 (25.2) | 13 (16) | 47 (21.8) | 0.115* |
| Normal | 101 (74.8) | 68 (84) | 169 (78.2) | |
| Mean 25-hydroxy vitamin D level ± SD | 26.01±7.97 | 26.18±6.69 | 29.10±7.34 | 0.054⁺ |

*p value obtained from Pearson chi-square or Fisher's exact test, ⁺p value obtained from Mann-Whitney U test. SD: Standard deviation

A significant difference was observed between the groups in the preference for medical information sources on social media ($p<0.001$). Among individuals influenced by social media, 51.9% relied on non-medical social media influencers, compared with 16.3% in the independent group ($p<0.001$). Conversely, 39.3% of participants in the independent group preferred patient platforms, compared with only 8.6% of participants in the social media group. No statistically significant differences were observed between groups in general well-being, adverse effects, or duration of vitamin supplementation ($p>0.05$; Table 1).

The mean vitamin B12 level of the patients included in the study was 338.62±104.68 pg/mL. In the group that initiated vitamin supplementation on their own, the mean level was 333.31±116.02 pg/mL; in the social media-influenced group, it was 343.93±92.21 pg/mL. Vitamin B12 deficiency was significantly more common among patients who used supplements independently than among those influenced by social media ($p=0.022$). No significant differences between groups were observed in vitamin D levels or deficiencies ($p>0.05$) (Table 1).

The usage rates of social media channels among the 216 participants are presented in Table 2. The vast majority (97.2%) reported using search engines (e.g., Google, Yandex) to obtain information. Among social media platforms, Instagram was the most frequently used (84.7%), followed by Twitter (70.4%), YouTube (62.5%), Facebook (34.7%), personal blogs (28.2%), and TikTok (9.3%). Among the 81 individuals who began using vitamin supplements under the influence of social media, Instagram was the preferred platform (33.3%), followed by Twitter (19.8%), YouTube (16%), TikTok (12.4%), search engines such as Google (9.9%), and Facebook (8.6%) (Table 2).

**Table 2. Social media usage habits among individuals using vitamin complexes**

| | **n (%)** |
|---|---|
| **Social media subtypes (n=216)** | |
| Search engines (Google, Yandex, etc.) | 210 (97.2) |
| Instagram | 183 (84.7) |
| Youtube | 135 (62.5) |
| TikTok | 20 (9.3) |
| Personal blogs | 61 (28.2) |
| Twitter (now known as X) | 152 (70.4) |
| Facebook | 75 (34.7) |
| **Which social media channel did you use to start vitamin supplementation? (n=81)** | |
| Twitter (now known as X) | 16 (19.8) |
| Instagram | 27 (33.3) |
| Facebook | 7 (8.6) |
| TikTok | 10 (12.4) |
| Youtube | 13 (16) |
| Google search engine | 8 (9.9) |
| n=216 | |

## Discussion

Vitamin deficiencies in adults represent a significant health issue that can negatively impact quality of life (9). Today, such deficiencies are far more common than many might expect. To address this, individuals aware of the issue often turn to OTC products and dietary supplements, integrating them into their daily routines to pursue a healthier lifestyle without medical supervision.

In 2018, a multicenter study conducted across 18 European countries evaluated the public's knowledge and awareness of the health effects of OTC medications and dietary supplements. The study found that 68% of patients regularly consumed at least one OTC medication or dietary supplement. The frequency of use of at least one OTC product or supplement varied by country. The most commonly used products were vitamins (38%), minerals (34%), cranberry juice (20%), acetylsalicylic acid (17%), and omega fatty acids (17%). Among the 18 participating European countries, Türkiye had the highest proportion of patients using at least one OTC product (94%). This finding highlights a high propensity for, and limited awareness of, OTC product use among the Turkish population (10). In our study, we found that 37.5% (n=81) of the participants had started using vitamin supplements solely because of promotion on social media.

In a 2003 Canadian study involving 306 patients with a history of cardiovascular disease, two-thirds of the participants reported using at least one OTC product per week. The most commonly used products were pain relievers (51%), antacids (21%), and laxatives (17%). Two-thirds of the participants stated that they had used OTC products at least once per week in the past six months. Additionally, multivitamins or multivitamin-mineral products were consumed at least once daily by 23% of study participants during that period (11). These studies demonstrate the frequency with which OTC products are used and obtained without a prescription in developed countries, including European countries and Canada. Therefore, identifying the channels through which individuals choose these products is important; our study focuses on social media as one such channel.

With the increasing influence of the internet and social media, patients are turning to online platforms to access health-related information. While social media provides quick, easy, and practical access to valuable resources, it also exposes users to misleading and inaccurate content (12). In a 2022 study titled "The Use of Vitamin D in COVID-19: A YouTube Study," 77 videos with a total of 10,225,763 views were analyzed. Over three-quarters of these videos contained misleading information regarding the use of vitamin D in coronavirus disease-2019. Interestingly, the primary contributors were medical professionals who maintained YouTube channels. The study found that many of the recommendations in these videos were inconsistent with current literature, including suggestions to take vitamin D supplements at doses exceeding the recommended safe levels or to deliberately expose oneself to ultraviolet radiation (13). Similarly, in a study titled "YouTube as an Information Source on the Effect of Vitamin C on Coronavirus Disease," the 50 most-viewed videos on the subject were analyzed. The study found that 54% of the videos were unreliable, 62% were low quality, and 74% were

misleading (14). Thus, it is concerning that 37.5% of patients in our study rely on social media to decide on their vitamin intake.

In Germany, Instagram is the most popular social network, and many influencers use this platform to promote dietary supplements. A recent study investigated the dietary supplements promoted by influencers on Instagram in Germany (15). The study revealed significant shortcomings in the labeling of overdose risks and potential side effects. The findings indicate that Instagram is not a reliable platform for obtaining accurate information about dietary supplements. Due to its popularity and wide audience reach, concerns have been raised about misinformation and misguidance within the community. Our study also supports these concerns: 33.3% of participants who used OTC vitamin supplements after exposure to social media reported that Instagram influenced their decision.

Another study investigated the impact of influencer marketing on the use of dietary supplements among social media users in Türkiye. The study found that influencers play a critical role in product promotion because of their substantial follower bases and the trust they have established with their audiences. The findings indicated that following social media influencers and spending more time on social media significantly increased the likelihood of using dietary supplements. The study revealed that individuals who followed influencers were approximately 18 times more likely to use dietary supplements than those who did not (16). Similar findings were observed in our study, with 64 participants (29.6%) reporting that social media influencers were their most recent source of medical information. This finding underscores the substantial role of influencers in online sales of OTC products in Türkiye and highlights their significant impact on public health.

In our research, the majority of patients reported that their most recent source of medical information on social media was medical doctors' accounts or professional websites. This finding highlights the potential of social media platforms as powerful tools that enable physicians to educate their patients and contribute to public health. A study found that social media use was widespread among the patient group, and that potentially misleading information on these platforms was a matter of concern (17).

In our study, four of 216 participants reported drug-related side effects and subsequently discontinued use of the product. Usually, the promotional content of OTC products advertised on social media platforms does not provide sufficient information regarding potential side effects. Influencers and product promoters, primarily driven by commercial interests, often emphasize the positive effects of these products, thereby influencing the public toward those products. Crucial information regarding daily doses, costs, side effects, contraindications, and overdose risks is inadequately addressed by influencers (15).

Vitamin D and B12 deficiencies are more prevalent in the population than expected. A study at a tertiary care hospital in our country demonstrated that both B12 deficiency and falsely elevated B12 levels are associated with critical illness, which further highlights the importance of accurately measuring vitamin B12 and vitamin D levels (18). The prevalence of B12 deficiency reaches 40% in Latin America, 70% in Africa, and 70-80% in South Asia (19). Similarly, vitamin D deficiency is estimated to affect 30% to 50% of the global population (20).

Despite being common health problems readily diagnosed by routine laboratory tests, these vitamin deficiencies often remain inadequately addressed. Our study found that vitamin D deficiency was present in both groups: those who independently used OTC vitamin supplements and those were influenced by social media. Notably, despite vitamin supplementation, 21.8% of the 216 participants in our study had 25-(OH)D levels below the deficiency threshold. One possible explanation for this persistent deficiency could be insufficient vitamin D content in multivitamin complexes or a limited absorption capacity. Another contributing factor may be that many of these supplements are not approved by the Ministry of Health but by the Ministry of Agriculture, which allows them to be rapidly marketed and sold online without stringent quality control. Based on these findings, healthcare professionals should measure vitamin D levels using serum 25-(OH)D testing. When a deficiency is detected, personalized treatment protocols should be implemented to achieve optimal vitamin D levels in patients, taking into account their vitamin D status and risk factors (21).

Vitamin B12 deficiency was identified in 6% of the patients included in our study. However, the majority of participants had adequate serum vitamin B12 levels. Vitamin B12 deficiency was significantly less common among patients whose use of vitamin supplements was influenced by social media than among patients in the other group. This may be explained by the finding that the group of vitamin supplement users influenced by social media most frequently initiated supplementation based on recommendations from medical doctor accounts or websites, suggesting that they were more likely to choose an appropriate product.

### Study Limitations

The cross-sectional design of this study limits causal inference. Conducted at a single center with a relatively small sample, this study's findings may have limited generalizability. In addition, reliance on self-reported data for social media use and supplement intake may introduce recall bias.

## Conclusion

Over the years, it has become increasingly accepted that social media and the internet significantly influence public health. Although social media often provides individuals with easy access to information, it also contains content and product promotions that may negatively impact health. Ensuring the accuracy of health-related information on these platforms and promoting physician-guided use of supplements are crucial for safeguarding public health. Further regulation of online health content and influencer marketing practices is needed to minimize the risks associated with unsupervised supplement use.

### Ethics

**Ethics Committee Approval:** Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (approval number: 234, date: 12.09.2025).

**Informed Consent:** The informed consent was obtained through institutional procedures, and all patient data were anonymized prior to analysis.

**Footnotes**

**Authorship Contributions:** Concept - Y.G., G.Y., B.K.K., M.A., M.E.P.; Design - Y.G., İ.C.Ç., M.O.T., M.E.P.; Data Collection or Processing - Y.G., G.Y., İ.C.Ç., M.O.T.; Analysis or Interpretation - Y.G., B.K.K., M.O.T., M.A., M.E.P.; Literature Search - Y.G., G.Y., İ.C.Ç., B.K.K., M.A.; Writing - Y.G.

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# Which is The Best Timing for Ultrasound-Guided Transversus Abdominis Plane Block During Laparoscopic Cholecystectomy: Preoperative or Postoperative?

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## ABSTRACT

**Introduction:** In biliary operations, laparoscopic techniques have largely replaced traditional methods; cholecystectomy is among the most common. Despite being minimally invasive, this procedure still poses a notable challenge in managing postoperative pain. This study aims to examine the impact of administering the transversus abdominis plane (TAP) block either before or after surgery on pain levels and hemodynamic responses in patients undergoing laparoscopic cholecystectomy.

**Methods:** A total of 75 cases were retrospectively reviewed, all of whom had undergone a laparoscopic cholecystectomy and received a bilateral TAP block under ultrasound guidance. Participants were divided into two cohorts: the TAP block was administered to Group 1 before surgery and to Group 2 after surgery. Evaluated variables included demographic data, numerical pain scales, hemodynamic indicators, patient-controlled analgesia (PCA) device utilization, opioid requirements, and postoperative symptoms.

**Results:** Group 1 consisted of 35 patients. American Society of Anesthesiologists grading, body mass index, surgery length, and demographic characteristics such as age and sex were statistically similar in both patient groups. Intraoperative hemodynamic parameters were also similar ($p>0.05$). The amount of remifentanil administered during surgery was considerably greater in those assigned to Group 2 ($p=0.001$). Pain intensity assessed at 0 and 1 hours after surgery was markedly lower in Group 1 than in Group 2 ($p<0.05$). No statistically significant difference in PCA usage was found between the groups ($p>0.05$). Nevertheless, patients in Group 2 required considerably more opioid analgesics in addition to PCA at postoperative hours 0 and 1 ($p=0.036$ and $p=0.040$, respectively). Furthermore, nausea occurred more frequently in Group 2 at the second postoperative hour ($p=0.040$).

**Conclusion:** This study demonstrates that preoperative TAP block administration during laparoscopic cholecystectomy reduces intraoperative opioid requirements, lowers early postoperative pain scores, and decreases the need for additional postoperative opioid analgesia compared with postoperative TAP block administration.

**Keywords:** Transversus abdominis plane block, laparoscopic cholecystectomy, postoperative analgesia

## Introduction

Because it is less invasive and offers quicker recovery than open procedures, laparoscopic cholecystectomy is now the most widely adopted method in biliary surgery (1). Persistent postoperative pain represents a substantial barrier to optimal early recovery, and when poorly addressed, it can lead to long-term complications, including chronic pain syndromes and prolonged hospitalization (2). The current standard of care for postoperative pain management is multimodal analgesia, which includes non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and regional nerve blocks (3). Although opioids are potent analgesics, their use is limited by adverse effects, including itching, respiratory depression, nausea, and vomiting (4). Likewise, NSAIDs are linked to significant complications such as cardiac issues, kidney impairment, and gastrointestinal problems (5). In this context, regional nerve blocks provide multiple benefits, such as reducing dependence on systemic analgesics and decreasing complications associated with their use. Additionally, these blocks contribute to maintaining hemodynamic stability, promoting early mobilization and discharge, enhancing patient satisfaction, and reducing overall hospital costs (6).

In 2001, Rafi (7) described the transversus abdominis plane (TAP) block as a method of regional anesthesiain which local anesthetic is delivered into the fascial space between the internal oblique and transversus abdominis muscles. The injection is guided by identifying the anatomical landmark referred to as the triangle of Petit. This approach primarily targets the

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anterior branches of thoracic nerves T7-T12 and the first lumbar nerve (8). As ultrasound (US)-guided techniques have become more common in clinical practice, the TAP block has proven effective in minimizing opioid requirements during and after surgeries such as laparotomy, appendectomy, cesarean delivery, and laparoscopic cholecystectomy (9). The duration of pain relief provided by the TAP block can last up to 24 hours and varies depending on the type of anesthetic agent administered (10). Although it can be applied at different points in the perioperative period, existing research offers limited insight into the optimal timing for its administration.

This study explores how the timing of US-guided TAP block administration at different perioperative stages influences intraoperative hemodynamic stability, opioid requirements, postoperative pain levels, and total analgesic consumption in patients undergoing laparoscopic cholecystectomy.

## Methods

### Compliance with Ethical Standards

The study was approved by the Ethics Committee of Tokat Gaziosmanpaşa University (approval number: 25-MOBAEK-001, date: 07.01.2025).

### Study Design

The study retrospectively examined individuals who underwent laparoscopic cholecystectomy between January 1 and December 30, 2024, and who received bilateral TAP blocks under US guidance for postoperative pain control, in addition to receiving patient-controlled analgesia (PCA). Data were retrieved from the institutional hospital database. Only patients aged 18-75 years and classified as American Society of Anesthesiologists (ASA) class I-III were included in the study.

Patients were grouped according to when the TAP block was applied.

In Group 1, the bilateral TAP block was administered following endotracheal intubation but before the surgical procedure began.

In Group 2, the bilateral TAP block was administered immediately after the surgical procedure and just prior to extubation.

Additional regional anesthetic techniques, including spinal or epidural anesthesia, were not employed in any patient.

The primary endpoint of the study was the assessment of pain levels during the first 24 hours after surgery. Pain assessment was performed using the numeric rating scale (NRS) (11). In cases where the NRS score was 5 or higher, an NSAID was administered as the first-line additional analgesic. If pain persisted, a rescue analgesic consisting of 50 mg of intravenous tramadol was administered. All patients who received rescue analgesia were recorded. Pain management after abdominal surgery is routinely performed in this manner at our institution.

Secondary outcomes included intraoperative hemodynamic parameters, intraoperative opioid consumption, postoperative hemodynamic data within 24 hours, PCA usage metrics, additional opioid requirements, and postoperative nausea and vomiting.

Researchers analyzed and contrasted the primary and secondary outcomes observed in each group.

### TAP Block Technique and Pain Management

In this study, all patients received bilateral TAP blocks under US-guidance via a lateral approach. The procedures were performed by experienced anesthesiologists. According to our institutional protocol, TAP blocks were administered using 0.25% bupivacaine (Buvasin 0.5%, Vem İlaç, Türkiye), with 20 mL injected on each side, for a total of 40 mL of local anesthetic per patient. All patients included in the study underwent the standard procedure used in our routine clinical practice. Each patient received intravenous paracetamol (1 g) and dexketoprofen (50 mg) before extubation. Following extubation, a standardized PCA device was connected to each patient. After extubation, all patients received postoperative analgesia via a PCA pump prepared according to the standard procedure of our clinic. The content of the PCA bag consisted of 300 mg (6 mL) of tramadol diluted with normal saline to a total volume of 150 mL (2 mg/mL tramadol). According to the PCA protocol, patients could receive a 20-mg bolus of tramadol upon request without a continuous background infusion. The daily dose was capped at 400 mg, and the lockout interval was set at 20 minutes. Both pain intensity scores and PCA usage statistics were recorded using the institution's standardized pain monitoring form.

### Exclusion Criteria

Participants were excluded if they had missing data, used the PCA device improperly, had known opioid dependence or tolerance, had the laparoscopic procedure converted to an open procedure, had a history of abdominal surgery, underwent emergency procedures, required intraoperative blood transfusion or inotropic agents, or had preexisting hepatic or renal dysfunction.

### Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous data was assessed through the Shapiro-Wilk test. Data conforming to a normal distribution were presented as mean ± standard deviation, while non-normally distributed variables were described using medians with their corresponding minimum and maximum values. Categorical variables were summarized as frequencies and percentages.

Depending on the distribution characteristics, different statistical tests were employed for group comparisons. Variables with a normal distribution were analyzed using the independent t-test, whereas variables that did not follow a normal distribution were analyzed using the Mann-Whitney U test. For categorical comparisons, either Fisher's exact test or Pearson's chi-square test was applied as appropriate.

## Results

The study population comprised 75 individuals, 35 of whom were assigned to Group 1. No statistically significant differences were observed between the groups with respect to ASA status, body mass index, duration of surgery, patient age, and gender distribution ($p>0.05$) (Table 1). No

substantial variation in intraoperative heart rate or in mean arterial pressure was observed between the two groups (p>0.05) (Graphic 1). Regarding intraoperative remifentanil consumption, the mean values were 86.11±153 mcg in Group 1 and 446.7±632 mcg in Group 2, indicating significantly higher consumption in Group 2 (p=0.001).

Statistical analysis revealed a clear disparity in postoperative pain levels across the study cohorts. At rest, Group 2 reported considerably pain levels than Group 1 at both the immediate (0-hour) and 1-hour time points following surgery (p<0.001 and p=0.005, respectively; Table 2). A similar pattern was observed during coughing, where Group 2 again reported higher pain scores at the same time intervals (p<0.001 and p=0.006, respectively; Table 3). No statistically significant differences were identified between the groups at subsequent time points, either at rest or during coughing (p>0.05).

Analysis of PCA-device data revealed comparable results across groups in terms of analgesic request frequency, bolus administrations, and total analgesic use during the first 24 hours (p>0.05; Table 4).

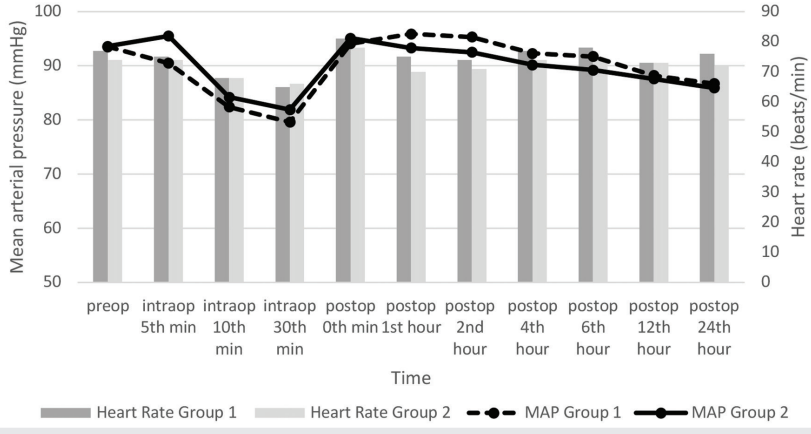
However, analysis of additional opioid administration beyond PCA revealed that patients in Group 2 had significantly higher opioid requirements at 0 and 1 hours postoperatively (p=0.036 and p=0.040, respectively; Table 5).

Assessment of nausea and vomiting following surgery indicated a higher incidence of nausea in Group 2 at the second hour (p=0.040; Table 6). Despite this, no significant difference between groups was observed in the frequency of postoperative vomiting (p>0.05).

**Table 1. Demographic characteristics and duration of surgery**

| | Group 1 | Group 2 | p |
|---|---|---|---|
| Age (years) | 50.9±16.1 | 45.2±15.4 | 0.126[a] |
| Sex (male/female) | 21 (60%)/14 (40%) | 16 (40%)/24 (60%) | 0.084[b] |
| BMI (kg/m$^2$) | 27.27±2.86 | 26.93±2.49 | 0.562[a] |
| ASA 1 | 6 (17%) | 5 (12.5%) | 0.510[b] |
| 2 | 20 (57%) | 28 (70%) | |
| 3 | 9 (26%) | 7 (17.5%) | |
| Duration of surgery (minimum) | 79.9±16.4 | 75.1±18.3 | 0.235[a] |

Data are presented as mean ± standard deviation or number of patients (%). [a]Independent samples t-test; [b]Pearson chi-square test
BMI: Body mass index, ASA: American Society of Anesthesiologists




**Graphic 1.** Intergroup comparison of mean arterial pressure and heart rate

**Table 2. Intergroup comparison of numeric rating scales at rest**

| | Group 1 | Group 2 | p[a] |
|---|---|---|---|
| 0$^{th}$ hour | 3.00 (0–7) | 4.00 (0–10) | **<0.001*** |
| 1$^{st}$ hour | 3.00 (0–7) | 4.00 (1–9) | **0.005*** |
| 2$^{nd}$ hour | 3.00 (0–7) | 3.00 (0–9) | 0.532 |
| 4$^{th}$ hour | 2.00 (0–7) | 2.00 (0–6) | 0.790 |
| 6$^{th}$ hour | 1.00 (0–5) | 2.00 (0–5) | 0.278 |
| 12$^{th}$ hour | 1.00 (0–5) | 1.00 (0–5) | 0.409 |
| 24$^{th}$ hour | 0.00 (0–4) | 1.00 (0–5) | 0.061 |

*Significant difference at <0.05 level according to Mann-Whitney U test, Data are presented as median (min-max), [a]Mann-Whitney U test

**Table 3. Intergroup comparison of numeric rating scales at cough**

| | Group 1 | Group 2 | p[a] |
|---|---|---|---|
| 0$^{th}$ hour | 4.00 (0–8) | 5.00 (0–10) | **<0.001*** |
| 1$^{st}$ hour | 4.00 (0–8) | 5.00 (1–9) | **0.006*** |
| 2$^{nd}$ hour | 4.00 (0–8) | 4.00 (0–9) | 0.444 |
| 4$^{th}$ hour | 3.00 (0–8) | 3.00 (0–7) | 0.897 |
| 6$^{th}$ hour | 2.00 (0–6) | 2.00 (0–6) | 0.527 |
| 12$^{th}$ hour | 2.00 (0–7) | 2.00 (0–6) | 0.427 |
| 24$^{th}$ hour | 2.00 (0–5) | 2.00 (0–6) | 0.172 |

*Significant difference at <0.05 level according to Mann-Whitney U test, Data are presented as median (min-max), [a]Mann-Whitney U test

**Table 4. Comparison of patient-controlled analgesia usage data between groups**

| | Group 1 | Group 2 | p[a] |
|---|---|---|---|
| Number of demands | 18.34±10.99 | 19.75±10.52 | 0.573 |
| Number of boluses | 10.83±5.08 | 11.55±3.96 | 0.493 |
| Requested dose (mg) | 361.14±211.76 | 395.0±210.43 | 0.490 |
| Delivered dose (mg) | 213.71±101.83 | 228.5±81.88 | 0.488 |

All values expressed as mean ± standard deviation, [a]Independent samples t-test

**Table 5. Comparison of the number of patients receiving additional intravenous rescue opioids**

| | Group 1 (n=35) | Group 2 (n=40) | p |
|---|---|---|---|
| 0 hour | 3 (8.6%) | 11 (27.5%) | **0.036**[a] |
| 1st hour | 2 (5.7%) | 9 (22.5%) | **0.040**[a] |
| 2nd hour | 1 (2.9%) | 2 (5.0%) | 0.637[a] |
| 2–4 hours | 1 (2.9%) | 1 (2.5%) | 0.924[a] |
| 4–8 hours | 0 | 1 (2.5%) | 0.346[a] |
| 8–16 hours | 1 (2.9%) | 0 | 0.467[b] |
| 16–24 hours | 1 (2.9%) | 1 (2.5%) | 0.924[a] |

[a]Pearson chi-square test, [b]Fisher's exact test

**Table 6. Comparison of the number of patients experiencing postoperative nausea between groups**

| | Group 1 (n=35) | Group 2 (n=40) | p |
|---|---|---|---|
| 0th hour | 3 (8.6%) | 8 (20.0%) | 0.163[a] |
| 1st hour | 2 (5.7%) | 5 (12.5%) | 0.438[b] |
| 2nd hour | 2 (5.7%) | 9 (22.5%) | **0.040**[a] |
| 4th hour | 1 (2.9%) | 2 (5.0%) | 0.637[a] |
| 6th hour | 2 (5.7%) | 2 (5.0%) | 0.891[a] |
| 12th hour | 4 (11.4%) | 3 (7.5%) | 0.699[b] |
| 24th hour | 1 (2.9%) | 0 | 0.467[b] |

[a]Pearson chi-square test, [b]Fisher's exact test

## Discussion

Our findings suggest that administering a bilateral TAP block under US guidance at different time points notably affects early postoperative outcomes after laparoscopic cholecystectomy. Individuals who received a TAP block before surgery reported lower pain levels at 0 and 1 hour after the operation, compared with those who received the block postoperatively. Moreover, patients in the preoperative TAP block group required significantly less remifentanil during surgery. In addition, the use of intravenous rescue opioids was markedly reduced in this group.

TAP block is an essential component of multimodal analgesic strategies for laparoscopic abdominal surgery. Previous research has shown that it is superior to control groups, providing better pain relief and reducing the need for postoperative analgesics after abdominal surgery. By reducing opioid consumption, the TAP block helps mitigate undesirable side effects associated with opioids (12). Although TAP blocks are commonly employed in abdominal surgeries, the ideal timing for their application remains a subject of debate among researchers. Depending on institutional practice and surgical planning, the block may be administered at various time points. Previous literature indicates that TAP block administration is feasible at various stages, including before induction of general anesthesia, immediately before the skin incision while under general anesthesia, or immediately after the surgical procedure while the patient remains under general anesthesia (13). Other studies have also explored the effectiveness of TAP block when applied at different time intervals during spinal anesthesia (14). This investigation categorized patients into two cohorts: one received the TAP block after endotracheal intubation and before surgery began; the other received it after the operation, prior to extubation.

Delivering analgesia in advance of surgical trauma, referred to as preemptive analgesia, may help diminish postoperative pain severity by limiting central nervous system sensitization and decreasing pain signal transmission from peripheral sites. Nonetheless, the existing literature offers differing perspectives on the optimal timing for TAP block application. In a meta-analysis by Dost et al. (15), studies of TAP block in laparoscopic cholecystectomy were reviewed; studies in which the block was administered postoperatively showed more favorable outcomes. In contrast, De Oliveira et al. (9) reported in their meta-analysis that application of a preoperative TAP block led to lower early postoperative pain levels and reduced opioid use in laparoscopic abdominal procedures. Despite such evidence, few studies have directly examined how the timing of TAP block affects outcomes within the same patient cohort. For example, Rahimzadeh et al. (16) conducted a comparative analysis of TAP block timings in laparoscopic cholecystectomy and reported that postoperative pain levels and opioid consumption did not vary meaningfully across TAP block timings. On the other hand, Dirican et al. (17) reported that performing the TAP block postoperatively alleviated early postoperative pain in women who underwent total abdominal hysterectomy. Although another study comparing TAP block timings showed no significant difference in early postoperative pain, it noted that patients who underwent the procedure before the surgical incision experienced less pain after the second postoperative hour (18). Another study involving inguinal hernia surgery also demonstrated superior early pain control in the pre-incisional TAP block group (19). Consistent with previous research, the current analysis revealed a clear reduction in early postoperative pain among individuals who underwent a preoperative TAP block. Differences in results reported across studies may be attributed to variations in local anesthetic type and dosage. For example, Rahimzadeh et al. (16) used a different local anesthetic from that used in our study, while Amr and Amin (18) administered a higher dose; these differences may explain the differing outcomes. Although Dirican et al. (17) used a similar dosage, we believe that variations in surgical duration might have influenced the results. Bhanushree et al. (20) observed that delivering the TAP block before surgery yielded more favorable outcomes than administering it afterward, particularly in abdominal procedures lasting under 180 minutes. Consistent with Shim et al. (19), the surgical duration in our study was relatively short compared with other reports.

Preoperative administration of peripheral nerve blocks is believed to reduce intraoperative opioid requirements by inducing central desensitization (21). In our study, an infusion of remifentanil was employed as part of the anesthetic regimen to counteract stress-induced

hemodynamic responses. Shim et al. (19) reported that remifentanil use during surgery was markedly reduced in patients who received the TAP block prior to incision. Our findings are consistent and show decreased intraoperative remifentanil requirements in the same group. Earlier studies have indicated a correlation between elevated intraoperative remifentanil administration and a heightened requirement for additional postoperative pain relief (22). This phenomenon has been attributed to remifentanil-induced postoperative hyperalgesia. In our study, the higher remifentanil consumption observed in Group 2 may explain the increased requirement for rescue analgesia during the immediate postoperative period. Additionally, as the TAP block contributes to reduced total opioid consumption during laparoscopic cholecystectomy, it may indirectly affect the frequency of postoperative nausea and vomiting. The increased nausea observed during the early postoperative phase in patients who received the TAP block after the surgical incision might be linked to their greater reliance on supplemental opioid analgesics.

### Study Limitations

Our study has several limitations. The study was conducted retrospectively, and because the TAP blocks were administered under general anesthesia, the exact level of sensory blockade could not be assessed. Additionally, the study lacked a control group, and the evaluation was limited to the first postoperative day. On the other hand, factors influencing the anesthesia team's preferences for the timing of block administration could not be determined.

## Conclusion

Our findings suggest that administering the TAP block before the incision phase in laparoscopic cholecystectomy contributes to reduced intraoperative opioid use, improved early pain control, and reduced need for rescue opioid analgesics compared with its application after the surgical incision. We believe that identifying the optimal timing for its administration and validating it through prospective, randomized studies would make a meaningful contribution to the literature.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Tokat Gaziosmanpaşa University (approval number: 25-MOBAEK-001, date: 07.01.2025).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - V.K., A.T.Ş., M.G.B., A.G., B.K.; Concept - V.K., A.T.Ş., M.G.B.; Design - V.K., M.G.B., A.G., B.K.; Data Collection or Processing - V.K., A.T.Ş., M.G.B., A.G., B.K.; Analysis or Interpretation - V.K., A.T.Ş.; Literature Search - V.K., A.G.; Writing - V.K., A.T.Ş., M.G.B., A.G., B.K.

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# Impact of The COVID-19 Pandemic on Carbapenem and Colistin Resistance of Gram-Negative Bacteria Isolated from Laboratory-Confirmed Healthcare-Associated Infections in Intensive Care Units

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## ABSTRACT

**Introduction:** The coronavirus disease 2019 (COVID-19) pandemic may have influenced antibiotic usage patterns. In particular, increased empirical use of broad-spectrum agents may have affected bacterial resistance profiles. This study aimed to evaluate the impact of the COVID-19 pandemic on carbapenem and colistin resistance in Gram-negative bacteria (GNB) isolated from laboratory-confirmed healthcare-associated infections (HAIs) in adult intensive care units (ICUs).

**Methods:** This retrospective study evaluated microbiological and antimicrobial resistance data across three consecutive time periods: Period 1 (March 2018–March 2020), Period 2 (March 2020–March 2022), and Period 3 (March 2022–March 2024). The carbapenem and colistin resistance profiles of GNB isolated from HAIs in ICU patients were assessed across these time frames.

**Results:** In Period 1, *Pseudomonas aeruginosa* was the most frequently isolated pathogen. In Period 2, *Acinetobacter baumannii* became predominant, while in the post-pandemic period, *Klebsiella pneumoniae* emerged as the leading pathogen. The rates of carbapenem-resistant *K. pneumoniae* (CRKP) (p=0.0007) and *P. aeruginosa* (CRPA) (p=0.0001) increased during the pandemic and remained elevated in Period 3. The rate of carbapenem-resistant *A. baumannii* remained unchanged across all periods. Colistin resistance in *A. baumannii* (p=0.0002) and *K. pneumoniae* (p=0.0063) increased significantly in Period 2. Colistin resistance in *P. aeruginosa* remained stable in Period 2, but increased in Period 3 (p=0.0019).

**Conclusion:** CRKP and CRPA became more prevalent during and after the COVID-19 pandemic, while colistin resistance among key ICU pathogens also increased. These findings suggest that pandemic-related changes in ICUs and antimicrobial use may have facilitated the persistence of highly resistant GNB. Continuous local surveillance and reinforcement of infection-control and stewardship programs are needed.

**Keywords:** COVID-19, Gram-negative bacteria, carbapenem resistance, colistin resistance

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a profound impact on healthcare systems worldwide. The sudden increase in hospitalization rates necessitated a rapid response to manage the increasing patient load in healthcare facilities (1). Intensive care units (ICUs) have been particularly affected by the frequent requirement for ventilatory support among patients with COVID-19. This situation has significantly increased demand for ICU beds and supplies, necessitating the reallocation of resources. However, the combination of increased demand and a shortage of healthcare professionals may have adversely affected certain operations and disrupted long-standing practices aimed at preventing healthcare-associated infections (HAIs). Considering factors, such as the rapid increase in ICU capacity, decreased staff-to-patient ratios, longer patient stays, and greater patient complexity, the risk of infection is likely to increase because of cross-contamination among patients (2). The COVID-19 pandemic may also have affected antibiotic consumption, contributing to increased antimicrobial resistance (AMR). Studies have shown that despite low rates of confirmed bacterial infections, the use of broad-spectrum antibiotics is common in patients with COVID-19 (3-5). Additionally, compliance with antibiotic stewardship programs has decreased during this period as healthcare providers struggle to save the lives of COVID-19 patients (6).

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Over the past decade, a notable rise in resistance to many antimicrobial agents has been observed among *Enterobacterales (CRE), Pseudomonas aeruginosa,* and *Acinetobacter baumannii*. This increase in AMR in ICUs is primarily due to the spread of high-risk clones, which play a crucial role in the global emergence of multidrug-resistant (MDR) bacteria. The increased empirical use of antibiotics during the COVID-19 pandemic and disruption of infection prevention and control practices in exhausted healthcare systems may have led to a further increase in AMR globally (5,7-9). Despite several reports on HAIs during the COVID-19 era, few studies have specifically tracked AMR among predominant Gram-negative bacteria (GNB) to evaluate the impact of COVID-19 in ICUs (10-12). Local data are essential to guide empirical therapy and infection-control policies. This study aims to assess the impact of the COVID-19 pandemic on carbapenem and colistin resistance in GNB isolated from laboratory-confirmed HAIs in adult ICUs.

## Methods

This retrospective study was conducted at an academic tertiary care center comprising multiple ICUs with a total capacity of 80 beds. Data were analyzed across three distinct periods: Period 1 (March 2018–March 2020), Period 2 (March 2020–March 2022), and Period 3 (March 2022–March 2024). AMR to key antibiotics, including carbapenems and colistin, was evaluated among GNB isolated from HAIs in ICU patients.

Bacterial identification was performed using an automated VITEK 2 system (bioMérieux, France) and conventional microbiological methods. The Kirby-Bauer disk diffusion method and VITEK 2 system were employed to determine the AMR patterns of the isolated microorganisms. Extended-spectrum beta-lactamase positivity was assessed using a double-disk synergy test. Colistin susceptibility was determined based on the results of a broth microdilution test, in accordance with the recommendations of the European Committee on Antimicrobial Susceptibility Testing.

Standardized case definitions for HAIs. Inclusion criteria include adult patients aged 18 years and older who have been in hospital for 48 hours or more and are diagnosed with HAIs, such as ventilator-associated pneumonia (VAP), hospital-acquired pneumonia, urinary tract infection (UTI), and bloodstream infection (BSI) caused by GNB. Clinical samples included endotracheal aspirates, urine, and blood specimens. Exclusion criteria included patients under 18 years of age, those who had not been admitted to an adult hospital for at least 48 hours, and those without a diagnosis of HAI caused by GNB. Multiple ICU admissions for the same patient and cases identified as colonization without evidence of active infection were also excluded.

The study was approved by the Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (research protocol number: 2025.147.07.17, dated: July 29, 2025) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

### Statistical Analysis

Data obtained in the study were analyzed using SPSS v. 15.0 for Windows. Categorical variables were expressed as frequencies (n) and percentages (%). The chi-square test for trend was used to compare categorical variables across the pre-pandemic, pandemic, and post-pandemic periods. A p value $<0.05$ was considered significant.

## Results

During the study period (March 2018–March 2024), 804 bacteria were detected in the ICUs, of which 662 were Gram-negative. A total of 587 patients were included, of whom 327 (55.7%) were male. VAP was identified as the most common HAI across all periods, with 291 (43.9%) cases reported. Other HAIs, listed in order of frequency, included BSI with 229 (34.5%) cases and UTI with 83 (12.5%) cases.

Most isolated microorganisms were GNB (76.2%); of these, approximately two-thirds (61.8%) were non-fermentative. The most frequently isolated pathogens were *Acinetobacter baumannii* (33.9%), *Pseudomonas aeruginosa* (27.9%), and *Klebsiella pneumoniae* (23.0%). In Period 1, the most commonly isolated infectious agents in ICUs were *A. baumannii* and *P. aeruginosa*; in Period 2, *A. baumannii* remained the predominant agent. During Period 3, *K. pneumoniae* became the most frequently isolated agent. The distribution of GNB in HAIs in adult ICUs is shown in Table 1.

The prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) increased from 25% (9/36) in Period 1 to 53% (26/49) in Period 2 and to 62.5% (35/56) in Period 3 (p=0.0019). Similarly, carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) rose from 22% (16/73) to 46% (24/52) and to 65.2% (30/46) (p=0.0001). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) showed 100% across all periods.

Colistin-resistant *K. pneumoniae* increased significantly in Period 2, with rates of 2.8%, 34%, and 32.1% across the three periods (p=0.0063). Colistin resistance in *A. baumannii* increased from 1.6% in Period 1 to 8% in Period 2 and 23.9% in Period 3 (p=0.0002), while *P. aeruginosa* showed a delayed increase, from 1.3% in Period 1 and 1.9% in Period 2 to 15.2% in Period 3 (p=0.0019). Carbapenem and colistin resistance rates of the predominant GNB are summarized in Table 2.

## Discussion

HAIs are one of the most serious problems in medicine today, contributing to high mortality, prolonged hospital stays, and increased treatment costs. MDR bacteria are a significant cause of HAIs, especially in ICUs (13). Several studies have reported an increase in the prevalence of MDR bacteria and HAI rates, particularly in device-related infections, during the COVID-19 pandemic (8,9,14). In our study, *A. baumannii*, *P. aeruginosa,* and *K. pneumoniae* were the most frequently isolated GNB. Among them, A. baumannii consistently remained the predominant pathogen across all study periods. In Period 3, *K. pneumoniae* emerged as the most commonly isolated pathogen. CRPA and CRKP were higher during the pandemic than in the pre-pandemic period. During Period 3, CRPA and CRKP continued to increase. In this study, the proportion of resistant strains increased over the years. Possible reasons for this situation include overuse of antibiotics and reduced infection-control measures.

The impact of the COVID-19 pandemic on HAI rates and the AMR in microorganisms remains a topic of debate. Increasing resistance to carbapenems in GNB is particularly concerning due to the lack of safe

**Table 1. Distribution of Gram-negative bacteria in healthcare-associated infections in adult intensive care units**

| | Period 1 (March 2018–March 2020) | Period 2 (March 2020–March 2022) | Period 3 (March 2022–March 2024) | Total | |
|---|---|---|---|---|---|
| | n | n | n | n | % |
| *Acinetobacter baumannii* | 62 | 100 | 46 | 208 | 31.5 |
| *Pseudomonas aeruginosa* | 73 | 52 | 46 | 171 | 25.8 |
| *Klebsiella pneumoniae* | 36 | 49 | 56 | 141 | 21.3 |
| *Escherichia coli* | 22 | 24 | 7 | 53 | 8.1 |
| *Stenotrophomonas maltophilia* | 12 | 14 | 6 | 32 | 4.8 |
| *Enterobacter cloaceae complex* | 7 | 5 | 3 | 15 | 2.3 |
| *Enterobacter aerogenes* | 6 | 3 | 1 | 10 | 1.6 |
| *Proteus mirabilis* | 5 | 2 | 0 | 7 | 1.1 |
| *Serratia marcescens* | 3 | 3 | 1 | 7 | 1.1 |
| *Klebsiella oxytoca* | 3 | 2 | 1 | 6 | 0.9 |
| *Citrobacter* spp. | 1 | 1 | 1 | 3 | 0.5 |
| *Aeromonas sobria* | 1 | 0 | 0 | 1 | 0.1 |
| *Ochrobactrum anthropi* | 1 | 0 | 0 | 1 | 0.1 |
| *Delftia acidovorans* | 1 | 0 | 0 | 1 | 0.1 |
| *Sfingomonas paucimobilis* | 2 | 0 | 0 | 2 | 0.3 |
| *Morganella morganii* | 0 | 1 | 0 | 1 | 0.1 |
| *Pantoe agglomerans* | 0 | 1 | 0 | 1 | 0.1 |
| *Raoultella planticola* | 0 | 1 | 0 | 1 | 0.1 |
| *Acromobacter* spp. | 0 | 0 | 1 | 1 | 0.1 |
| Total | 235 | 258 | 169 | 662 | 100.0 |

**Table 2. Carbapenem and colistin resistance of the most frequently isolated Gram-negative bacteria**

| Microorganism/resistance | Period 1 (March 2018–March 2020) | | Period 2 (March 2020–March 2022) | | Period 3 (March 2022–March 2024) | | p value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| *Acinetobacter baumannii* | | | | | | | |
| Carbapenem resistance | 62 | 100.0 | 100 | 100.0 | 46 | 100.0 | - |
| Colistin resistance | 1 | 1.6 | 8 | 8.0 | 11 | 23.9 | 0.0002 |
| *Pseudomonas aeruginosa* | | | | | | | |
| Carbapenem resistance | 16 | 22.0 | 24 | 46.0 | 30 | 65.2 | 0.0001 |
| Colistin resistance | 1 | 1.3 | 1 | 1.9 | 7 | 15.2 | 0.0019 |
| *Klebsiella pneumoniae* | | | | | | | |
| Carbapenem resistance | 9 | 25.0 | 26 | 53.0 | 35 | 62.5 | 0.0007 |
| Colistin resistance | 1 | 2.8 | 17 | 34.0 | 18 | 32.1 | 0.0063 |

and effective alternative treatment options. In recent years, carbapenem-resistant *Enterobacterales* (CRE) have been reported worldwide, and their prevalence has dramatically increased in many countries. An increase in CRE infections in ICUs during the COVID-19 pandemic has also been reported (11,12). In a retrospective study, CRE colonization increased from 6.7% in 2019 to 50% in March–April 2020 (15). In a survey conducted in Wuhan, China, *A. baumannii* and *K. pneumoniae* were the most frequently isolated GNB. Carbapenem resistance rates for these bacteria were 91.2% and 75.5%, respectively (16). *Acinetobacter* species emerged as the predominant pathogens among COVID-19 patients who contracted HAIs, representing 22.3% of cases (17). A study from Brazil showed that *P. aeruginosa* (29.4%), *K. pneumoniae* (22.7%), and *A. baumannii* (15.9%) were the main MDR GNB isolated from patients in ICUs with COVID-19 (18). In a study from Türkiye, *A. baumannii* was the most common microorganism and *P. aeruginosa* the second most common, both before and during the COVID-19 pandemic; *A. baumannii* was an essential cause of HAIs in ICUs before and during the pandemic (10).

AMR is expected to remain a substantial threat to healthcare systems in the future. By 2050, an estimated 10 million people will die annually from antibiotic-resistant bacterial infections (19). Even before the COVID-19 pandemic, infections caused by MDR CREs, *P. aeruginosa,* and *A. baumannii* constituted a significant global public health concern because of limited effective antimicrobial options and the high lethality of these infections. This situation likely deteriorated during the pandemic, with hospitalized COVID-19 patients frequently

necessitating extended ICU stays and invasive procedures (16). In their study, Antunes et al. (20) reported that carbapenem resistance increased during the pandemic period. Although carbapenem resistance decreased after the pandemic, resistance rates remained higher than in the pre-pandemic period (20). According to our findings, carbapenem- and colistin-resistant GNB increased during the pandemic and in the post-pandemic period. During the pandemic and post-pandemic, there was an increase in infections caused by carbapenem and colistin-resistant GNB. It was thought that factors such as shortages of personnel in ICUs during the first year of the pandemic and personnel exhaustion due to long, demanding working hours adversely affected the rates of HAIs.

While the World Health Organization classified *P. aeruginosa* as a critical-priority pathogen in its 2017 list because of its carbapenem resistance, CRPA was reclassified into the high-priority group in the updated 2024 Bacterial Priority Pathogens List (21). However, we observed a continued increase in CRPA strains at our hospital during the study periods. This trend highlights a significant local concern that contrasts with the global reprioritization. The rising resistance in our setting may be attributed to local factors such as increased antibiotic pressure, prolonged ICU stays, and challenges in infection control. These findings underscore the importance of complementing global priority lists with local surveillance data to guide empiric therapy and infection control strategies effectively.

The increase in infections caused by resistant microorganisms, possibly related to a surge in antimicrobial use during the COVID-19 pandemic, highlights the seriousness of the AMR problem. Although the increase in carbapenem and colistin resistance during the pandemic and post-pandemic periods was notable, molecular typing was not performed in this study. However, based on the available data, there was no strong evidence to suggest clonal transmission, and the situation was therefore not considered an outbreak. While a rise in resistant isolates was observed within similar time frames, this increase did not appear to be linked to a single dominant strain. Instead, it is more likely attributable to various external factors, such as increased antibiotic pressure, lapses in infection control, or the introduction of resistant strains from different sources. The absence of clonal spread supports the hypothesis that the rise in resistance was multifactorial and system-driven, rather than due to in-hospital dissemination of a particular clone. From a public health perspective, these data support the reimplementation of strict hand-hygiene audits, environmental cleaning, and device-associated infection bundles in ICUs. Periodic feedback of unit-specific resistance rates to clinicians may improve empiric prescribing. Integration of antimicrobial stewardship with surge-capacity planning for future outbreaks is also recommended.

### Study Limitations

This study has several limitations. First, its retrospective, single-center design inherently limits generalizability to other institutions or healthcare settings. Data reflect local epidemiology, which may differ significantly between regions and hospitals. Second, the analysis was limited to carbapenem and colistin resistance; susceptibilities to other clinically relevant antimicrobial agents such as ceftazidime-avibactam, tigecycline, or fosfomycin were not assessed. Third, molecular typing of resistant isolates was not performed; thus, clonal relatedness and potential in-hospital transmission dynamics could not be assessed. Although no outbreak was suspected based on phenotypic data, the absence of genotyping limits the ability to confirm or exclude clonal dissemination.

## Conclusion

Carbapenem and colistin resistance among GNB in ICUs increased during the COVID-19 pandemic and remained high thereafter, especially in *K. pneumoniae* and *P. aeruginosa*, while CRAB was already highly prevalent. These findings indicate that pandemic-related pressure on ICUs may have accelerated the selection and transmission of highly resistant strains. Strengthening antimicrobial stewardship, restoring full infection-prevention bundles, and continuing local resistance surveillance are critical to limiting further spread.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (research protocol number: 2025.147.07.17, dated: July 29, 2025).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Concept - M.N.Ö., İ.E.; Design - M.N.Ö., İ.E.; Data Collection or Processing - M.N.Ö., M.D., İ.Y., İ.E.; Analysis or Interpretation - M.N.Ö., İ.E.; Literature Search - M.N.Ö., M.D., İ.Y., İ.E.; Writing: M.N.Ö., M.D., İ.Y., İ.E.

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# Comparison of Microsatellite Instability (MSI) and Microsatellite Stable (MSS) Invasive Breast Carcinoma Cases In Terms Of Neoadjuvant Chemotherapy Response, ER/PR Status, CerbB2, and Ki-67

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## ABSTRACT

**Introduction:** Microsatellite instability (MSI) is a well-established biomarker in certain malignancies; however, its prognostic and predictive role in breast cancer remains unclear. This study aimed to compare invasive breast carcinoma cases with MSI and those with microsatellite stability (MSS) regarding response to neoadjuvant chemotherapy (NACT), estrogen and progesterone receptor status, c-erbB-2 (CerbB2) expression, Ki-67 proliferation index, and clinicopathological features, using immunohistochemical (IHC) assessment of mismatch repair (MMR) protein expression.

**Methods:** Eighty-seven patients with invasive breast carcinoma who had received NACT were retrospectively analyzed. MMR protein expression was evaluated by IHC for MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). Clinicopathological and IHC variables, including Miller–Payne classification, Pinder lymph node response, hormone receptor status, Ki-67, and CerbB2 expression, were compared between MSI and MSS groups. Survival analyses were performed using the Kaplan–Meier method.

**Results:** MSI was detected in 8% of patients (7/87). Loss of nuclear expression was observed in MLH1/PMS2 (3 cases, 42%), MSH2/MSH6 (2 cases, 29%), and isolated PMS2 (2 cases, 29%). No significant differences were found between the MSI and MSS groups in terms of chemotherapy response, clinicopathological variables, or overall survival and disease-free survival ($p>0.05$).

**Conclusion:** MSI was identified in 8% of invasive breast carcinoma cases but showed no significant association with NACT response, clinicopathological features, or survival outcomes. Its prognostic and predictive role in breast cancer remains uncertain and warrants confirmation in larger prospective studies.

**Keywords:** Mismatch repair, microsatellite instability, neoadjuvant chemotherapy, breast carcinoma, hormone receptors, Ki-67, CerbB2

## Introduction

Breast carcinoma represents the most prevalent malignancy among women. According to SEER reports, 316,950 new cases of breast carcinoma were diagnosed in 2025; the majority were locally advanced at presentation (1). Neoadjuvant chemotherapy (NACT) is the current standard therapeutic approach for locally advanced breast cancer (2). However, this disease entity is highly heterogeneous with respect to both treatment response and survival outcomes (3).

Deficiencies in mismatch repair (MMR) proteins in breast cancer highlight their critical role in DNA repair mechanisms and may facilitate the acquisition of resistance to chemotherapeutic agents by tumor cells. Consequently, MMR deficiency is considered a potential contributor to breast cancer progression (4).

Microsatellites are short repetitive DNA sequences, typically comprising repeat units of 1–6 base pairs, such as [A]n or [CA]n. The MMR system involves key proteins, including MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6), and postmeiotic segregation

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increased 2 (PMS2) (5). Microsatellite instability (MSI), defined as random insertions or deletions resulting in alterations of microsatellite length, has been documented in a variety of tumor types (6).

Defects in the DNA MMR system are closely linked to the development of MSI; however, these entities are conceptually and diagnostically distinct. In normal cells, microsatellite sequences are maintained with high fidelity, whereas impaired MMR function allows replication-associated insertion–deletion errors to persist, resulting in alterations in microsatellite length. Accordingly, MSI represents a molecular consequence of defective MMR activity, while immunohistochemical (IHC) evaluation of MMR protein expression and assessment of MSI status reflect related but non-equivalent biological and diagnostic approaches (5).

The identification of MSI in multiple classes of malignancies has contributed to the broader adoption of immunotherapeutic strategies, which are presumed to be particularly effective against tumors harboring a high mutational burden and/or neoantigen load. DNA sensing mechanisms in cancer cells are essential for antitumor immune responses associated with *MMR* gene status, thereby offering novel avenues and biomarkers for immunotherapy (7).

MMR proteins are widely expressed molecules that play fundamental roles in diverse cellular processes, most notably in preserving genomic stability by correcting replication errors through post-replicative repair mechanisms. MMR deficiency has been associated with tumorigenesis and disease progression. This study aimed to investigate the relationship between MSI status and response to NACT, estrogen receptor (ER) and progesterone receptor (PR) status, c-erbB-2 (CerbB2) status, and Ki-67 expression in invasive breast carcinoma.

## Methods

### Definition of the Study Group

Ninety-five cases diagnosed with invasive breast carcinoma by tru-cut breast biopsy and who subsequently received neoadjuvant therapy and underwent breast resection were included in the study. Approval for the study was obtained from the Non-Interventional Scientific Research Ethics Committee of İstanbul Atlas University (approval number: 08/06, date: 29.09.2025). Eight cases were excluded because clinical data or access to pathology slides and paraffin blocks in the pathology laboratory were unavailable. Patient age and survival information were retrieved from hospital electronic medical records, while data on tumor size, tumor localization, and axillary lymph node status were obtained from radiological imaging and pathology reports.

### Histomorphologic Evaluation

In the 87 cases in our study group, hematoxylin and eosin-stained slides prepared from tru-cut biopsy specimens obtained prior to NACT and from breast resection specimens following NACT were reviewed by a single pathologist. The response of the tumor to neoadjuvant therapy in the breast resection specimens was evaluated according to the Miller and Payne classification (2003) (8) and categorized into one of five grades. According to the Miller and Payne classification, Grade 1 (no response/minimal response) is defined as no reduction in tumor cells following chemotherapy, or a reduction of less than 30%. Grade 2 (mild response): a reduction of 30–90% in tumor cells, but with readily identifiable residual tumor cells. Grade 3 (moderate response): More than 90% reduction in tumor cells, with a small number of viable cells remaining. Grade 4 (good response): Only small clusters of tumor cells or single cells remain. Grade 5 (complete response): No residual invasive tumor cells (only an *in situ* ductal component may remain) (8).

The axillary lymph node response to neoadjuvant therapy was evaluated according to the Pinder classification (2007) (9) and assigned to one of four categories (10). According to the Pinder classification: Pinder 1: No metastatic tumor and no therapeutic response in lymph nodes; Pinder 2: No metastatic tumor with therapeutic response in lymph nodes (e.g., fibrosis); Pinder 3: Metastatic tumor present with therapeutic response in lymph nodes; Pinder 4: Metastatic tumor present without therapeutic response in lymph nodes.

The histological type of the tumors in the tru-cut biopsy specimens was assessed according to the 2019 World Health Organization criteria. Histological grade and nuclear grade were determined using the Modified Scarff-Bloom-Richardson/Nottingham grading system (1991) (11). During histomorphological evaluation, carcinoma *in situ* and necrosis were recorded in the tru-cut biopsy specimens.

The stromal lymphocytic response around the tumor in tru-cut biopsy specimens was evaluated according to the recommendations of the International TILs Working Group (2014) (12). Based on these recommendations, lymphocytic response was graded as follows: Grade 1: <10%; Grade 2: ≥10%; Grade 3: ≥40%.

### Immunohistochemical Evaluation

IHC analysis was performed for the following markers: ER (Scyek, Rabbit, class: IgG1-kappa, clone: ERa078, dilution: 1:100); PR (Scyek, Human, class: IgG1-kappa, clone: PGR-1A6, dilution: 1:100); Ki67 (BioGenex, Mouse, class: IgG1-kappa, clone: BGX-Ki67, dilution: 1:100); CerbB2 (Thermo, Mouse, class: IgG1, clone: e2-4001 + 3B5, dilution: 1:400); MLH1 (Ventana, Mouse, clone: M1, ready-to-use); MSH2 (Ventana, Mouse, clone: G219-1129, ready-to-use); MSH6 (Ventana, Mouse, clone: SP93, ready-to-use); and PMS2 (Ventana, Mouse, clone: A16-4, ready-to-use). The evaluation of ER and PR staining was conducted in accordance with the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (10), with positivity defined as nuclear staining in ≥1% of invasive tumor cells. CerbB2 expression was assessed according to the 2018 ASCO/CAP guidelines and scored 0 (negative), 1+ (negative), 2+ (equivocal), or 3+ (positive) (13).

The Ki67 proliferation index was assessed following the international recommendations established by the Breast Cancer Study Group in 2011. Three high-power fields (× 40 magnification) from the invasive tumor area were selected, and the mean nuclear labeling index was calculated. In heterogeneous tumors, one of the three fields was designated as a hot spot, and the mean was calculated accordingly (14). Values ≥15% were considered high, and values were considered low.

MSI was defined as the absence of nuclear staining for at least one of the MLH1, MSH2, MSH6, or PMS2 antibodies in tumor cells, whereas microsatellite stability (MSS) was defined as focal or diffuse nuclear

staining for all four antibodies. Normal colonic mucosa, inflammatory cells, and stromal cells served as internal positive controls (4).

### Statistical Analysis

The distribution of the data was assessed using the Shapiro–Wilk test. For variables not conforming to a normal distribution, comparisons between two independent groups were performed with the Mann–Whitney U test. Comparisons of categorical variables between groups were evaluated using Fisher's exact test or the chi-square test, as appropriate. Overall survival and disease-free survival by group were analyzed using the Kaplan–Meier method, and differences were assessed with the log-rank test. Descriptive statistics for continuous variables were expressed as means [standard deviations (SDs)] and medians (minimum–maximum), whereas categorical variables were presented as frequencies (percentages). In survival analysis, descriptive statistics for overall survival and disease-free survival were reported as mean (standard error). All statistical analyses were conducted using IBM SPSS Statistics version 29.0.2 with a significance level set at $p<0.05$.

## Results

### General Characteristics of the Findings

A total of 87 patients were included in the study. The mean age of the patients was 51.69 (10.88) years (range: 31–74). The mean overall survival was 48.39 (28.63) months (range: 2–108 months), and the mean disease-free survival was 46.98 (31.57) months (range: 0–108 months). At the last follow-up, 17 patients (19.5%) were alive, and 70 patients (80.5%) were deceased.

Histopathological evaluation of resection specimens revealed 75 cases (86.2%) of invasive ductal carcinoma, 8 cases (9.2%) of invasive lobular carcinoma, and 4 cases (4.6%) of mixed histology. Tumor localization was in the right breast in 43 patients (49.4%) and in the left breast in 44 patients (50.6%). The mean tumor size was 30.89 (15.29) mm (range: 9.5–86 mm). Fine-needle aspiration cytology of the axilla showed negative results in 14 patients (19.4%) and positive results in 58 patients (80.6%), while radiological evaluation of the axilla revealed negative findings in 10 patients (11.6%) and positive findings in 76 patients (88.4%). Radiological multifocality was detected in 25 patients (28.7%); the mean number of foci was 2.76 (SD: 1.09; range: 2–6).

Histological grading demonstrated Grade 1 in 6 patients (10.5%), Grade 2 in 35 patients (61.4%), and Grade 3 in 16 patients (28.1%). Nuclear grades were distributed as follows: Grade 1 in 5 patients (8.8%), Grade 2 in 28 patients (49.1%), and Grade 3 in 24 patients (42.1%). Lymphovascular invasion (LVI) was present in 30 patients (34.5%) and perineural invasion (PNI) was present in 17 patients (19.5%). Ductal carcinoma *in situ* was identified in 34 cases (39.1%), while lobular carcinoma *in situ* was observed in 2 cases (2.3%).

IHC evaluation revealed ER positivity in 50 patients (89.3%) and ER negativity in 6 patients (10.7%). PR was positive in 43 patients (76.8%) and negative in 13 patients (23.2%). CerbB2 expression was negative in 38 patients (66.7%) and positive in 19 patients (33.3%). The distribution of CerbB2 scores was as follows: 0 in 25 patients (43.9%), 1 in 13 patients (22.8%), 2 in 2 patients (3.5%), and 3 in 17 patients (29.8%).

According to the Miller–Payne grading system, 7 patients (8%) were Grade 1 (no or minimal response), 13 (14.9%) were Grade 2 (minimal response; 30–90% reduction in tumor cells), 23 (26.4%) were Grade 3 (moderate response; >90% reduction in tumor cells), 14 (16.1%) were Grade 4 (good response; small clusters or isolated tumor cells), and 30 (34.5%) were Grade 5 (complete response; no viable tumor cells).

Based on the Pinder classification, 28 patients (32.6%) were Grade 1 (no metastatic tumor and no treatment response in lymph nodes), 10 (11.6%) were Gade 2 (no metastatic tumor and treatment response in lymph nodes such as fibrosis), 33 (38.4%) were Grade 3 (metastatic tumor present and treatment response in lymph nodes), and 15 (17.4%) were Grade 4 (metastatic tumor present and no treatment response in lymph nodes).

The mean Ki-67 proliferation index was 28% (SD: 20%; range, 2–85%). Seven cases (8%) demonstrated MSI, whereas 80 cases (92%) were MSS. Among the MSI cases, loss of MLH1/PMS2 nuclear expression was detected in 3 patients (42%), loss of MSH2/MSH6 nuclear expression in 2 patients (29%), and isolated loss of PMS2 nuclear expression in 2 patients (29%). The results are summarized in Table 1.

### Microsatellite Instability Status

The results of statistical comparisons between the MSI group (Figure 1) and the MSS group with respect to the Miller–Payne classification; the Pinder lymph node scoring system; ER, PR, Ki67, CerbB2, and CerbB2 score (each assessed in resection and biopsy specimens); molecular subtype; stromal lymphocyte percentage and grade; intratumoral lymphocytic response; overall survival; disease-free survival; recurrence or metastasis; and mortality status are presented in Table 2. As shown in Table 2, no statistically significant differences were observed between groups for these variables ($p>0.05$). The distribution of molecular subtypes according to MSI status is illustrated in Figure 2.

The results of the statistical comparisons between the MSS and MSI groups in terms of tumor size, histological subtype, age, localization, quadrant, number of foci, histological grade, nuclear grade, LVI, PNI, and *in situ* components in the resection specimens are presented in Table 3. As shown in Table 3, none of these variables demonstrated statistically significant differences between the groups ($p>0.05$).

Similarly, statistical comparisons between MSS and MSI groups in biopsy specimens with respect to histological subtype, histological grade, nuclear grade, LVI, PNI, *in situ* components, and necrosis are summarized in Table 4. No statistically significant differences were observed between the groups for these biopsy-related variables ($p>0.05$).

Kaplan–Meier analysis was performed to evaluate overall survival and disease-free survival according to MSI and MSS status (Table 5, Figure 3). As shown in the table, overall survival did not differ significantly between the MSS and MSI groups ($p=0.659$). Disease-free survival according to MSI status is presented in Table 6; similarly, no statistically significant difference was found between the MSS and MSI groups ($p=0.806$) (Figure 4).

## Discussion

Breast cancer remains the leading cause of cancer-related mortality worldwide and demonstrates marked heterogeneity in its

**Table 1. Demographic, clinical, and pathological characteristics of patients included in the study**

| Variable | Value |
|---|---|
| Demographic data | |
| Descriptive statistics | |
| Number of patients | n=87 |
| Age (years) | 51.69±10.88 (31–74) |
| Overall survival (months) | 48.39±28.63 (2–108) |
| Disease-free survival (months) | 46.98±31.57 (0–108) |
| Survival status | |
| Alive | 17 (19.5) |
| Dead | 70 (80.5) |
| Resection subtype | |
| IDC | 75 (86.2) |
| Lobular | 8 (9.2) |
| Mixed | 4 (4.6) |
| Localization | |
| 1 | 43 (49.4) |
| 2 | 44 (50.6) |
| Pathology IIAB | |
| Negative | 14 (19.4) |
| Positive | 58 (80.6) |
| Radiological axilla | |
| Negative | 10 (11.6) |
| Positive | 76 (88.4) |
| Radiological multifocality | |
| Absent | 62 (71.3) |
| Present | 25 (28.7) |
| Histological grade | |
| 1 | 6 (10.5) |
| 2 | 35 (61.4) |
| 3 | 16 (28.1) |
| Nuclear grade | |
| 1 | 5 (8.8) |
| 2 | 28 (49.1) |
| 3 | 24 (42.1) |
| LVI | |
| Absent | 57 (65.5) |
| Present | 30 (34.5) |
| PNI | |
| Absent | 70 (80.5) |
| Present | 17 (19.5) |
| *In situ* | |
| 0 | 51 (58.6) |
| 1 | 34 (39.1) |
| 2 | 2 (2.3) |
| ER status | |
| Positive | 50 (89.3) |
| Negative | 6 (10.7) |
| PR status | |
| Positive | 43 (76.8) |
| Negative | 13 (23.2) |
| CerbB2 status | |
| Negative | 38 (66.7) |
| Positive | 19 (21.8) |
| CerbB2 score | |
| 0 | 25 (43.9) |
| 1 | 13 (22.8) |
| 2 | 2 (3.5) |
| 3 | 17 (29.8) |
| Miller–Payne | |
| 1 | 7 (8) |
| 2 | 13 (14.9) |
| 3 | 23 (26.4) |
| 4 | 14 (16.1) |
| 5 | 30 (34.5) |
| Pinder | |
| 1 | 28 (32.6) |
| 2 | 10 (11.6) |
| 3 | 33 (38.4) |
| 4 | 15 (17.4) |
| Tumor size (mm) | 30.89±15.29 (9.5–86) |
| Number of foci | 2.76±1.09 (2–6) |
| Ki-67 (%) | 0.28±0.20 (0.02–0.85) |

Data are presented as frequency (percentage) or mean ± standard deviation (minimum-maximum), IDC: Invasive ductal carcinoma, IIAB: Fine needle aspiration biopsy, LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor, PR: Progesterone receptor, CerbB2: c-erbB-2

histopathology, molecular biology, and response to systemic therapies (1). As in many other malignancies, breast cancer has been classified into distinct subtypes to enable the development and implementation of tailored therapeutic regimens. Among the diverse forms of genetic damage, including DNA double-strand breaks, base substitutions, and mismatches, such alterations represent some of the most detrimental lesions that threaten cellular viability. To safeguard genomic stability, cells have evolved multiple repair pathways, the disruption of which plays a pivotal role in breast carcinogenesis (15).

One of these critical repair pathways is the DNA MMR system, which recognizes and corrects misincorporated bases that occur during DNA replication, recombination, or as a result of other genotoxic insults. The MMR system additionally addresses errors that escape the proofreading activity of DNA polymerase (16). Integrity of the MMR pathway is essential for maintaining genomic fidelity; however, given that several chemotherapeutic agents target this mechanism, tumors harboring MMR deficiency may acquire resistance, thereby complicating therapeutic strategies and adversely affecting clinical outcomes (17).

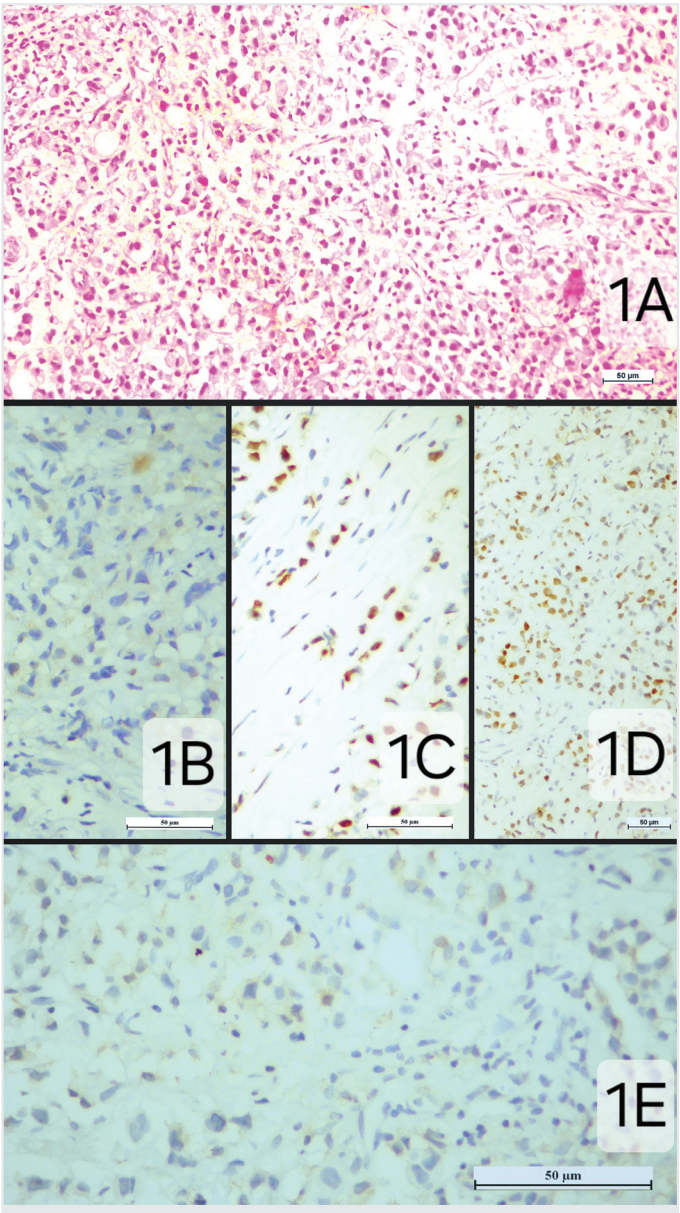


**Figure 1.** (A) Invasive ductal carcinoma (hematoxylin and eosin, × 200). (B) Loss of nuclear expression of PMS2 (IHC, × 400). (C) Nuclear staining for MSH2 (IHC, × 200). (D) Nuclear staining for MSH6 (IHC, × 400). (E) Loss of nuclear expression of MLH1 (IHC, × 400)

PMS2: Postmeiotic segregation increased 2, IHC: Immunohistochemistry, MSH2: MutS homolog 2, MSH6: MutS homolog 6, MLH1: MutL homolog 1

While MSI, a hallmark of defective MMR, has been extensively documented in colorectal, endometrial, and ovarian carcinomas, its prevalence, biological relevance, and prognostic value in breast carcinoma remain incompletely elucidated and are the subjects of ongoing investigation (18-21).

The aim of this study was to investigate the frequency of MSI in breast carcinoma and to evaluate its association with clinicopathological parameters. The findings of this study demonstrated that MSI had no significant correlation with clinicopathological variables or survival outcomes in breast carcinoma, suggesting that MSI may not be a strong prognostic or predictive biomarker in this tumor type.

**Table 2. Comparison of relevant variables between MSS and MSI groups**

| Variable | MSS | MSI | p |
|---|---|---|---|
| Miller–Payne | | | |
| 1 | 7 (100%) | 0 (0%) | |
| 2 | 13 (100%) | 0 (0%) | 0.802[a] |
| 3 | 20 (87.0%) | 3 (13.0%) | |
| 4 | 13 (92.9%) | 1 (7.1%) | |
| 5 | 26 (89.7%) | 3 (10.3%) | |
| Pinder | | | |
| 1 | 26 (92.9%) | 2 (7.1%) | |
| 2 | 9 (100%) | 0 (0%) | 0.842[a] |
| 3 | 29 (87.9%) | 4 (12.1%) | |
| 4 | 14 (93.3%) | 1 (6.7%) | |
| ER (resection) | | | |
| Negative | 6 (100%) | 0 (0%) | 1[a] |
| Positive | 46 (92.0%) | 4 (8.0%) | |
| PR (resection) | | | |
| Negative | 13 (100%) | 0 (0%) | 0.254[a] |
| Positive | 39 (90.7%) | 4 (9.3%) | |
| CerbB2 score (resection) | | | |
| Negative | 34 (89.5%) | 4 (10.5%) | 0.290[a] |
| Positive | 19 (100%) | 0 (0%) | |
| CerbB2 grade (resection) | | | |
| 0 | 23 (92.0%) | 2 (8.0%) | 0.358[a] |
| 1 | 11 (84.6%) | 2 (15.4%) | |
| 2 | 2 (100%) | 0 (0%) | |
| 3 | 17 (100%) | 0 (0%) | |
| ER (biopsy) | | | |
| Negative | 10 (100%) | 0 (0%) | 1[a] |
| Positive | 69 (90.8%) | 7 (9.2%) | |
| PR (biopsy) | | | |
| Negative | 26 (96.3%) | 1 (3.7%) | 0.425[a] |
| Positive | 53 (89.8%) | 6 (10.2%) | |
| Molecular subtype | | | |
| 1 | 11 (91.7%) | 1 (8.3%) | |
| 2 | 55 (90.2%) | 6 (9.8%) | 0.709[a] |
| 3 | 4 (100%) | 0 (0%) | |
| 4 | 9 (100%) | 0 (0%) | |
| Stromal lymphoid grade | | | |
| 1 | 42 (89.4%) | 5 (10.6%) | 0.634[a] |
| 2 | 22 (95.7%) | 1 (4.3%) | |
| 3 | 15 (93.8%) | 1 (6.3%) | |
| Survival status | | | |
| Dead | 16 (94.1%) | 1 (5.9%) | 0.704[a] |
| Alive | 63 (91.3%) | 6 (8.7%) | |
| CerbB2 score (biopsy) | | | |
| Negative | 43 (89.6%) | 5 (10.4%) | 0.457[a] |
| Positive | 36 (94.7%) | 2 (5.3%) | |

**Table 2. Continued**

| Variable | MSS | MSI | p |
|---|---|---|---|
| CerbB2 grade (biopsy) | | | |
| 0 | 22 (84.6%) | 4 (15.4%) | 0.456[a] |
| 1 | 20 (95.2%) | 1 (4.8%) | |
| 2 | 2 (100%) | 0 (0%) | |
| 3 | 35 (94.6%) | 2 (5.4%) | |
| Ki-67 (%) (resection) | 0.20 (0.02–0.85) | 0.30 (0.25–0.50) | 0.205[a] |
| Ki-67 (%) (biopsy) | 0.30 (0.10–0.80) | 0.30 (0.10–0.50) | 0.775[b] |
| Stromal lymphocytic response (%) | 0.20 (0.10–0.80) | 0.15 (0.10–0.90) | 0.346[b] |
| Overall survival (months) | 48 (2–108) | 60 (24–108) | 0.567[b] |
| Disease-free survival (months) | 42 (0–108) | 60 (24–108) | 0.542[b] |

Categorical data are presented as frequency (percentage), numerical data as median (minimum-maximum). [a]chi-square and [b]Mann Whitney U tests were used. MSS: Microsatellite stability, MSI: Microsatellite instability, ER: Estrogen receptor, PR: Progesterone receptor, CerbB2: c-erbB-2

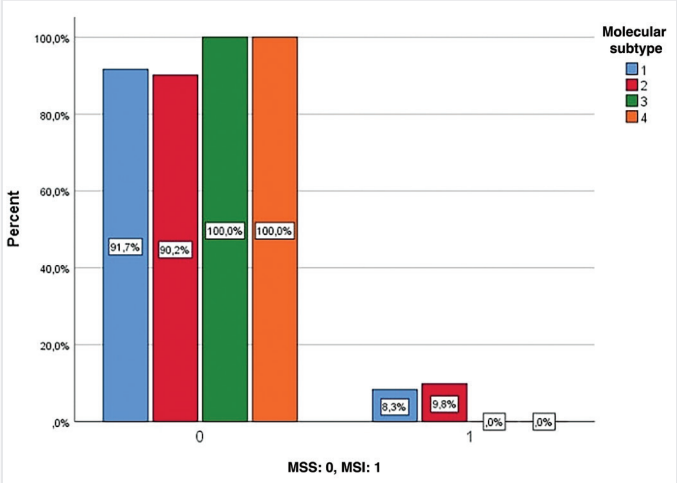


**Figure 2.** Distribution of molecular subtypes in MSS and MSI groups. Molecular subtype 1: Luminal A, 2: Luminal B, 3: Triple negative, 4: CerbB2
MSS: Microsatellite stability, MSI: Microsatellite instability, CerbB2: c-erbB-2

In our study, the prevalence of MSI was 8%, which is consistent with the findings reported in the literature (22). Data regarding the frequency of MSI in breast cancer are highly variable: some studies have reported a very low prevalence (below 1%), whereas others have documented higher rates, particularly in subtypes such as triple-negative breast cancer (23,24). For instance, one study conducted in patients with metastatic breast cancer reported an MSI prevalence of 0.63% (25). Such discrepancies may be attributed to factors including sample size, population heterogeneity, the methodologies employed for MSI detection, and differences in study design (26,27).

A large-scale study by Cheng et al. (28) that evaluated the relationship between MMR deficiency, breast cancer subtypes, and prognostic factors reported MMR deficiency in 1.9% of 1,635 cases assessed by immunohistochemistry. This study demonstrated that MMR deficiency was associated with a higher histological grade, lower PR expression, and a higher number of tumor-infiltrating lymphocytes. Moreover, among 431 ER–positive patients who received adjuvant systemic therapy with tamoxifen alone, MMR deficiency was significantly associated with poorer overall survival and disease-free survival (28). In contrast, our study found no statistically significant association between MMR status and histological grade, PR status, TIL percentage, or survival outcomes. The discrepancies between these findings may be attributed to differences in sample size, population characteristics, therapeutic approaches, and sampling methodologies.

**Table 3. Comparison of relevant variables between MSS and MSI groups in resection**

| Variable | MSS | MSI | p |
|---|---|---|---|
| Localization | | | |
| 1 | 38 (88.4%) | 5 (11.6%) | 0.433[a] |
| 2 | 41 (95.3%) | 2 (4.7%) | |
| Subtype | | | |
| IDC | 69 (93.2%) | 5 (6.8%) | 0.155[a] |
| Lobular | 6 (75%) | 2 (25%) | |
| Mixed | 4 (100%) | 0 (0%) | |
| Quadrant | | | |
| Upper inner | 10 (83.3%) | 2 (16.7%) | 0.197[a] |
| Upper outer | 41 (95.3%) | 2 (4.7%) | |
| Lower inner | 13 (81.3%) | 3 (18.7%) | |
| Lower outer | 12 (100%) | 0 (0%) | |
| Retroareolar | 3 (100%) | 0 (0%) | |
| Histological grade | | | |
| 1 | 5 (83.3%) | 1 (16.7%) | 0.554[a] |
| 2 | 33 (94.3%) | 2 (5.7%) | |
| 3 | 15 (93.8%) | 1 (6.3%) | |
| Nuclear grade | | | |
| 1 | 4 (80%) | 1 (20%) | 0.393[a] |
| 2 | 26 (92.9%) | 2 (7.1%) | |
| 3 | 23 (95.8%) | 1 (4.2%) | |
| LVI | | | |
| Absent | 50 (89.3%) | 6 (10.7%) | 0.413[a] |
| Present | 29 (96.7%) | 1 (3.3%) | |
| PNI | | | |
| Absent | 62 (89.9%) | 7 (10.1%) | 0.336[a] |
| Present | 17 (100%) | 0 (0%) | |
| *In situ* carcinoma | | | |
| 0 | 47 (94%) | 3 (6%) | 0.552[a] |
| 1 | 30 (88.2%) | 4 (11.8%) | |
| 2 | 2 (100%) | 0 (0%) | |
| Age (years) | 49 (31–74) | 59 (49–63) | 0.057[b] |
| Tumor size (mm, radiological) | 28 (9.5–86) | 29 (12–37) | 0.962[b] |
| Number of foci | 2.5 (2–6) | 2 (2–2) | 0.304[b] |

Categorical data are presented as frequency (percentage), numerical data as median (minimum-maximum). [a]chi-square and [b]Mann-Whitney U tests were used. MSS: Microsatellite stability, MSI: Microsatellite instability, LVI: Lymphovascular invasion, PNI: Perineural invasion, IDC: Invasive ductal carcinoma

**Table 4. Comparison of relevant variables between MSS and MSI groups in biopsy**

| Variable | MSS | MSI | p |
|---|---|---|---|
| Subtype | | | |
| IDC | 70 (92.1%) | 6 (7.9%) | 0.593[a] |
| Lobular | 6 (85.7%) | 1 (14.3%) | |
| Mixed | 3 (100%) | 0 (0%) | |
| Histological grade | | | |
| 1 | 6 (85.7%) | 1 (14.3%) | 0.365[a] |
| 2 | 49 (94.2%) | 3 (5.8%) | |
| 3 | 24 (88.9%) | 3 (11.1%) | |
| Nuclear grade | | | |
| 1 | 5 (83.3%) | 1 (16.7%) | 0.266[a] |
| 2 | 49 (94.2%) | 3 (5.8%) | |
| 3 | 25 (89.3%) | 3 (10.7%) | |
| LVI | | | |
| Absent | 55 (90.2%) | 6 (9.8%) | 0.668[a] |
| Present | 24 (96%) | 1 (4%) | |
| PNI | | | |
| Absent | 73 (91.3%) | 7 (8.8%) | 1[a] |
| Present | 6 (100%) | 0 (0%) | |
| *In situ* | | | |
| 0 | 64 (90.1%) | 7 (9.9%) | 0.653[a] |
| 1 | 13 (100%) | 0 (0%) | |
| 2 | 2 (100%) | 0 (0%) | |
| Necrosis | | | |
| Absent | 71 (92.2%) | 6 (7.8%) | 0.552[a] |
| Present | 8 (88.9%) | 1 (11.1%) | |

Categorical data are presented as frequency (percentage). [a]chi-square test was used. IDC: Invasive ductal carcinoma, LVI: Lymphovascular invasion, PNI: Perineural invasion, MSS: Microsatellite stability, MSI: Microsatellite instability

**Table 5. Evaluation of survival time according to MSI and MSS status**

| Group | Estimate | Standard error | 95% CI | p |
|---|---|---|---|---|
| MSS | 88.53 | 4.29 | 80.12–96.94 | 0.659 |
| MSI | 93.60 | 12.88 | 68.35–118.84 | |

p value corresponds to Log-Rank test. CI: Confidence interval, MSS: Microsatellite stability, MSI: Microsatellite instability

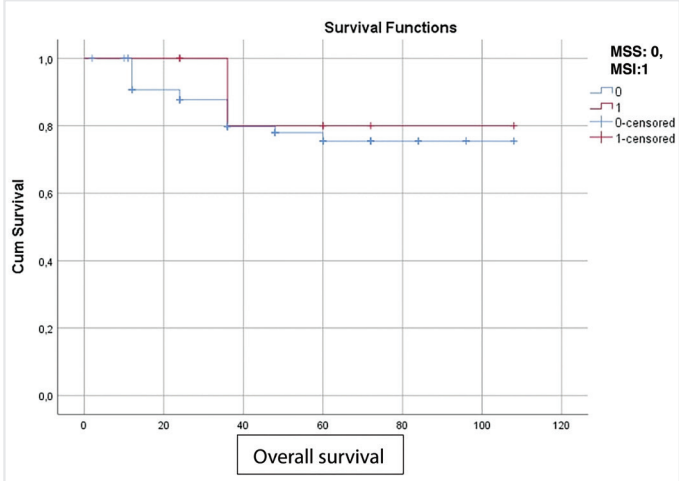


**Figure 3.** Overall survival according to MSI and MSS status
MSS: Microsatellite stability, MSI: Microsatellite instability

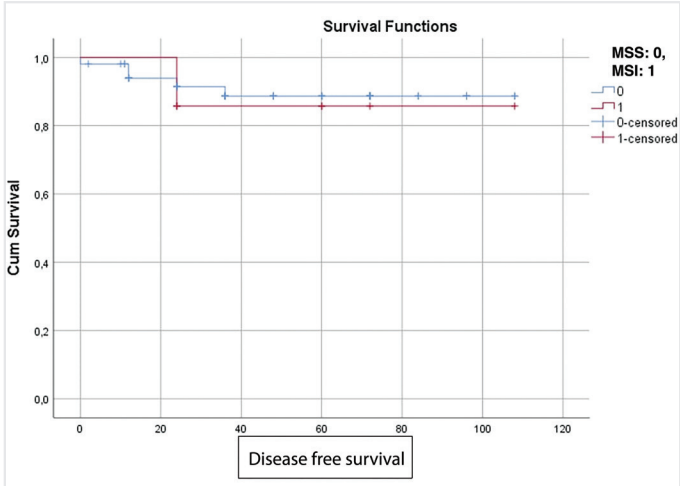


**Figure 4.** Disease-free survival according to MSI and MSS status
MSS: Microsatellite stability, MSI: Microsatellite instability

**Table 6. Evaluation of disease-free survival time according to MSI and MSS status**

| Group | Estimate | Standard error | 95% CI | p |
|---|---|---|---|---|
| MSS | 97.84 | 4.29 | 89.42–106.26 | 0.806 |
| MSI | 96 | 11.11 | 74.22–117.77 | |

p value corresponds to Log-Rank test. CI: Confidence interval, MSS: Microsatellite stability, MSI: Microsatellite instability

In the study by Cheng et al. (28), MSI status was not found to be highly prevalent in any specific molecular subtype of breast cancer. Similarly, in our study, no significant association was observed between MSI status and molecular subtypes, which is consistent with the existing literature.

Although some studies have suggested that MSI may be associated with chemotherapy response in breast cancer, our study did not identify any statistically significant association between MSI status and histopathological parameters before and after chemotherapy, nor between MSI status and survival outcomes (4). In the study by Demokan et al. (6), MSI was similarly found to have no significant association with age, lymph node involvement, disease stage, tumor size, ER status, metastasis, family history, or histological and nuclear grades. Consistent with these findings, our study demonstrated no statistically significant association between MSI status and age, tumor subtype, localization, multifocality, histological and nuclear grades, LVI, PNI, metastatic status, ER, PR, CerbB2, or Ki-67 proliferation index.

These parallel findings suggest that the biological mechanisms by which MSI may contribute to breast carcinogenesis are incompletely understood, and that its prognostic and predictive significance in this tumor type is uncertain. This supports the broader observation that the prognostic and predictive value of MSI may vary considerably across different cancer types (17,29).

A high degree of concordance between IHC and molecular techniques in the detection of MMR deficiency has been consistently reported. Several studies have indicated that both IHC and molecular assays are highly effective and equally informative (30). Although our study employed only the IHC method, the similarity between our findings and those reported in the literature suggests that IHC is a widely applicable, cost-effective, and diagnostically reliable alternative in clinical practice.

In our study, no statistically significant differences were observed between the MSI and MSS groups with respect to the Miller–Payne classification, Pinder lymph node scoring system, ER, PR, Ki67, CerbB2, CerbB2 score, molecular subtype, stromal lymphocyte percentage, stromal lymphocyte grade, intratumoral lymphocytic response, overall survival, disease-free survival, recurrence or metastasis, or mortality status. Assessments were performed on both tru-cut biopsies and post-neoadjuvant resection specimens ($p>0.05$). Similarly, statistical analysis of resection specimens revealed no significant differences between MSI and MSS groups with respect to tumor size, histological subtype, age, tumor localization (quadrant), number of foci, histological grade, nuclear grade, LVI, PNI, or presence of carcinoma *in situ* ($p>0.05$). Furthermore, analysis of biopsy specimens demonstrated no significant association between MSI status and histological subtype, histological grade, nuclear grade, LVI, PNI, *in situ* carcinoma, or necrosis ($p>0.05$). Overall survival and disease-free survival also did not differ significantly according to MSI or MSS status ($p>0.05$).

These findings support the conclusion that MMR/MSI is not a robust prognostic or predictive biomarker in breast cancer.

### Study Limitations

The main limitations of our study are its retrospective design and the relatively small sample size. Future research should aim to elucidate the role of MMR/MSI in breast cancer through larger, prospective cohort studies conducted in diverse ethnic populations that utilize standardized testing methodologies and evaluate specific chemotherapy regimens. In addition, the interactions between MMR status, the tumor microenvironment, and immune responses represent important areas that warrant further investigation.

## Conclusion

This study aimed to determine the frequency of microsatellite instability in invasive breast carcinoma and to evaluate its associations with response to NACT, clinicopathological parameters, and survival outcomes. In our cohort, MSI was identified in 8% of cases. The principal finding of our study is that MSI status did not show a statistically significant association with any evaluated clinicopathological variable, including the Miller–Payne classification, Pinder lymph node scoring system, ER and PR status, Ki-67 proliferation index, CerbB2 expression, molecular subtype, stromal lymphocyte percentage/grade, intratumoral lymphocytic response, tumor size, histological grade, or lymphovascular/perineural invasion, nor with survival outcomes, namely overall survival and disease-free survival. These results suggest that within our cohort of patients with invasive breast carcinoma, MSI does not emerge as an independent prognostic or predictive biomarker.

Although MSI is widely recognized as a strong prognostic marker and predictor of response to immunotherapy in certain cancers, its role in breast cancer appears to be more complex and remains insufficiently clarified. While some studies have suggested that loss of MMR protein expression may serve as a prognostic and predictive biomarker in breast cancer, the findings of our study support the view that evidence does not consistently demonstrate MSI as a reliable prognostic or predictive marker in this tumor type. Despite the retrospective design and limited sample size, our results indicate that immunohistochemistry can be used as a practical approach for evaluating MMR protein expression in routine pathology.

Future investigations should further clarify the role of MSI/MMR alterations in breast cancer through larger, prospective cohort studies employing standardized testing methodologies and assessing their relationship with specific NACT regimens. Such comprehensive studies may contribute to the development of more personalized therapeutic approaches in the management of breast cancer.

### Ethics

**Ethics Committee Approval:** Approval for the study was obtained from the Non-Interventional Scientific Research Ethics Committee of İstanbul Atlas University (approval number: 08/06, date: 29.09.2025).

**Informed Consent:** Retrospective study.

### Footnotes

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

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

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# Radiation Exposure in Thyroid Cancer Patients Treated with Radioiodine: A Dental Perspective

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## ABSTRACT

**Introduction:** This study aimed to experimentally determine radiation safety criteria for dentists who examine or treat patients receiving radioactive iodine (RAI) therapy for the follow-up of differentiated thyroid cancer in the nuclear medicine department.

**Methods:** Twenty-three patients undergoing whole-body scintigraphy with RAI were included. Each patient received 185 MBq of RAI orally on an outpatient basis and remained in lead-shielded isolation rooms for approximately two hours to allow for systemic distribution. Dose-rate measurements were then obtained along a horizontal line at distances of 5, 15, 30, 60, and 100 cm from the neck and abdominal regions.

**Results:** During the first 0–2 hours, mean dose rates measured from the neck at 5, 15, 30, 60, and 100 cm were 584±120 µSv/h, 312±52 µSv/h, 175±36 µSv/h, 18±6 µSv/h, and 11±4 µSv/h, respectively. Based on these data, the estimated radiation dose to a dentist during close contact (5–30 cm) was 224 µSv on the first day, 117 µSv on the second day, and 3 µSv on the third day after administration.

**Conclusion:** The permissible chairside exposure time on the first day was estimated at approximately 3.12 hours without exceeding safety limits. However, when daily dose limits derived from annual occupational exposure are considered, the third day after RAI administration was identified as the safer period for dental procedures

**Keywords:** Thyroid cancer therapy, radioiodine therapy, whole-body scan, dentist, radiation dose

## Introduction

Differentiated thyroid cancer (DTC) is one of the most common endocrine malignancies. Following total thyroidectomy, radioactive iodine (RAI) therapy has long been a fundamental approach for ablation of residual thyroid tissue and control of metastatic disease. Among the parameters used for post-ablation follow-up, whole-body scintigraphy (WBS) with iodine-131 ($^{131}$I) remains the most important and widely accepted imaging method. Serial $^{131}$I whole-body scans after ablation are still recognized in clinical guidelines as a key follow-up strategy (1,2).

$^{131}$I is a well-established theranostic radionuclide with a physical half-life of approximately eight days. It exerts its therapeutic effect through the emission of high-energy beta ($\beta^-$) particles (606-keV) and simultaneously enables diagnostic imaging with 364-keV gamma photons. Despite these valuable diagnostic advantages, RAI therapy can cause cytotoxic effects in healthy tissues and raise significant radiation safety concerns for healthcare workers, family members, and the general public (3).

In the nuclear medicine department, an oral dose of 74–185 MBq of $^{131}$I is routinely administered to patients undergoing whole-body scans on an outpatient basis after both written and verbal radiation safety instructions have been provided. Whole-body imaging is typically performed 24–72 hours later (4). These pre-administration instructions serve two main purposes: (i) to reduce the external radiation dose rate emitted by the patient and (ii) to minimize environmental contamination caused by radioactive materials excreted in urine, saliva, sweat, and other bodily secretions.

A considerable portion of the orally administered RAI remains within the patient's body after leaving the clinic. Over time, RAI is cleared through both physical decay and biological elimination. The residual radioactivity poses an external radiation hazard to individuals in close proximity and may cause contamination via body fluids. According to radiation protection regulations, the annual effective dose limit for the general public is 1 mSv (5,6). Consequently, discharged patients are advised to

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observe specific social restrictions: maintain physical distance, sleep in separate beds, practice strict personal hygiene (frequent handwashing), wash clothes separately, ensure toilet hygiene, avoid sharing kitchen utensils, and avoid contact with pregnant women and children (7).

Although RAI therapy has been widely used for decades, current radiation safety guidelines generally recommend maintaining at least 1 meter of distance from the patient and avoiding prolonged close contact. The International Commission on Radiological Protection (ICRP) Publication 60 report has set the annual radiation dose limits for members of the public at 1 mSv for adults and 0.5 mSv for children and pregnant women (6). Moreover, the As Low As Reasonably Achievable (ALARA) principle emphasizes keeping radiation exposure to a minimum that is reasonably achievable (8).

One of the most frequent post-discharge challenges arises when patients require unplanned medical or dental care shortly after RAI administration. For instance, a DTC patient who recently received RAI for whole-body imaging may develop severe dental pain and need to visit a dentist. In such situations, ensuring radiation safety requires that the patient's dose rate at a distance of 1 meter be below the regulatory release criterion so that any additional exposure to dental personnel during close contact does not exceed the annual public dose limit of 1 mSv. In principle, this condition allows for a safe dental examination. However, patients are advised to inform their dentist of recent RAI therapy, minimize unnecessary close contact, and, if possible, use lead aprons during treatment. Strict hygiene measures should be taken to prevent contamination through saliva, and elective dental procedures should be postponed for a short period when feasible.

During dental examination or treatment, a dentist typically works within 5–30 cm of the patient's oral region, while general communication and preparatory procedures typically occur at 60–100 cm. Despite the long-standing use of RAI therapy in DTC management, no dedicated experimental study has yet evaluated radiation safety considerations specific to dental professionals. Therefore, the present study was designed to determine experimentally the criteria necessary to ensure radiation safety for dentists who examine or treat DTC patients who were recently administered 185 MBq of RAI for outpatient WBS.

## Methods

This study was conducted at the radionuclide therapy unit of the department of nuclear medicine, Cerrahpaşa medical faculty. A randomly selected group of patients who were referred to the clinic for radioiodine (RAI) WBS as part of follow-up for DTC was included. All procedures were performed in strict accordance with the ethical principles outlined in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the İstanbul Kent University Clinical Research Ethics Committee (approval number: 2025-07, date: 10.09.2025). Written informed consent was obtained from all participants prior to inclusion in the study.

### Patient Population

A total of 23 patients (14 females and 9 males) were enrolled in this investigation. Each patient received 185 MBq of $^{131}$I orally on an empty stomach. All participants underwent treatment for DTC and were referred for a routine whole-body scan 6–12 months after therapy.

### RAI Administration and External Dose-Rate Measurement Technique from a Dental-Safety Perspective

Following both written and verbal radiation safety instructions, each fasting patient was orally administered 185 MBq of $^{131}$I. To ensure uniform biodistribution of radioiodine, patients remained in lead-shielded isolation rooms for approximately two hours. During this period, direct contact with visitors was strictly prohibited, and all patient care activities were carried out by certified radiation personnel following the time–distance–shielding principles.

Approximately two hours after administration, dose-rate measurements were performed at distances of 5, 15, 30, 60, and 100 cm from the patient's neck and abdomen, along a line parallel to the floor.

Dose rate measurements were performed using a validated and calibrated portable Geiger–Müller survey meter (Model 9DP, Ludlum), specifically verified for high-energy gamma emitters such as Cs-137. Calibration validity (May 2028); energy range: 60 keV to approximately 1.25 Mev.

In this study, a customized measurement protocol was developed to simulate a realistic dental examination environment. Prior to discharge, each patient was seated in a standard dental chair, with dose-rate measurements obtained from an anterior oblique position that represents the typical approach distance of a dentist during clinical practice. Patients were routinely recalled to the nuclear medicine department between days 1 and 3 post-RAI administration for WBS, during which additional dose-rate measurements were taken from the same neck-level reference points at distances of 5, 15, 30, 60, and 100 cm, measured parallel to the floor.

### Dose Calculation Method

The radiation detector measured dose rates at various distances, providing instantaneous dose values in µSv/h. During dose-rate measurements, conditions that closely resembled a patient's posture while sitting in the dental chair for a procedure were established. Additionally, measurements were performed under conditions simulating the dentist's typical position and approach distance while treating a patient. In this way, the geometric conditions during measurements were closely matched to those during actual dental procedures.

For converting these dose rates into cumulative doses, the following equation was used:

Dose (µSv) = dose rate (µSv/h) × procedure duration (h).

### Statistical Analysis

Dose-rate measurements obtained 30 cm from the neck and 30 cm from the abdomen were compared using the Wilcoxon paired test; $p \leq 0.05$ was considered statistically significant.

## Results

Before RAI therapy, stimulated thyroglobulin (Tg) levels were measured as part of the routine laboratory evaluation. Under thyroid stimulating

hormone (TSH) stimulation, Tg levels varied depending on tumor pathology and treatment activity. Among the 23 patients, TSH levels ranged from 34.2 to 142 µIU/mL (mean: 63.8 µIU/mL), and the mean Tg level was 1.98 ng/dL (range: 0.45–4.6 ng/dL). The mean pre-scan values of free T3 ($fT_3$), free T4 ($fT_4$), and TSH for all patients were 0.52±0.03 pg/mL, 0.36±0.07 ng/dL, and 64.8±16.8 µIU/mL, respectively (Table 1). Metastatic thyroid cancer was present in 4 of the 23 patients (17%).

The external dose rates measured at various distances from the patients are summarized in Tables 2 and 3 for the neck and abdominal regions, respectively. In both anatomical regions, the dose-rate values decreased sharply with increasing distance and with elapsed time after RAI administration. During the 0–2-hour period, the mean dose rates measured from the neck region were 584±120 µSv/h at 5 cm, 312±52 µSv/h at 15 cm, and 11±4 µSv/h at 100 cm. Based on these data, the cumulative radiation dose potentially received by a dentist during close contact (within a range of 5–30 cm) was estimated as 224 µSv initially, decreasing to 117 µSv on day 1 and to 3 µSv by day 3.

As shown in Figure 1, the cumulative exposure dose remained below the 1-mSv threshold, and the calculated exposure duration required to reach that limit on the first day was approximately 3.12 hours. Therefore, it can be concluded that provided standard radiation protection measures (such as wearing a lead apron and minimizing contact time) are strictly followed, dental examinations or interventions performed on the day of discharge do not pose a radiation safety risk to dentists treating patients who have received up to 185 MBq of $^{131}I$. However, when the daily public dose limit of 4 µSv/day is applied, the safe exposure level for dentists treating these patients is reached on the third day after RAI administration.

The correlation analysis between these mean dose rates is presented in Figure 2. The Pearson correlaton coefficient of determination ($R^2$: 0.9993) indicated a very strong correlation between external dose rates measured in the abdominal and neck regions. This finding indicates that changes in dose rate depend not only on the total administered activity but also on individual biological and physiological clearance factors, such as metabolic rate, the size of residual thyroid tissue, and the tissue distribution of RAI. Collectively, these results quantitatively define a practical safety margin for dental professionals. Patients who received less than 185 MBq of $^{131}I$ may be safely examined and treated for up to 3.12 hours, beginning two hours after discharge from the clinic, without exceeding the annual dose limit of 1 mSv. However, to ensure that dentists' radiation exposure remains below the daily public dose limit of 4 µSv, dental visits should be postponed for at least three days.

**Table 1. Demographic and thyroid cancer–specific clinical characteristics of patients scanning with radioactive iodine**

| Gender | Age | Weight | $fT_3$ | $fT_4$ | TSH |
|---|---|---|---|---|---|
| (n=23) | (years) | (kg) | (pg/mL) | (ng/dL) | (µIU/mL) |
| Female (n=14) | 58.2±21.1 | 63.5±7.9 | 0.32±0.01 | 0.41±0.05 | 61.2±11.3 |
| Male (n=9) | 64.3±17.2 | 73.7±12.0 | 0.72±0.08 | 0.32±0.03 | 66.5±12.2 |
| Normals | | | 2.0-4.4 | 0.93-1.7 | 0.27-4.2 |

$fT_3$: free $T_3$, $fT_4$: free $T_4$, TSH: Thyroid stimulating hormone

**Table 2. Dose rates measured from the neck region in thyroid cancer patients receiving 185 MBq radioactive iodine for diagnostic whole-body scanning**

| Distance (cm) | Day 0 (µSv/h) | Day 1 (µSv/h) | Day 3 (µSv/h) |
|---|---|---|---|
| 5 | 584±120 | 295±38 | 10±3 |
| 15 | 312±52 | 120±42 | 6±3 |
| 30 | 175±36 | 48±11 | 3±2 |
| 60 | 18±6 | 4±2 | 2±1 |
| 100 | 11±4 | 1±0.1 | 0.1±0.001 |

**Table 3. Dose rates measured from the abdomen region in thyroid cancer patients receiving 185 MBq radioactive iodine for diagnostic whole-body scanning**

| Distance (cm) | Day 0 (µSv/h) | Day 1 (µSv/h) | Day 3 (µSv/h) |
|---|---|---|---|
| 5 | 684±62 | 232±102 | 7±27 |
| 15 | 290±42 | 165±46 | 3±18 |
| 30 | 163±23 | 97±24 | 2±11 |
| 60 | 69±8 | 8±87 | 1±0.01 |
| 100 | 10±3 | 4±2 | 0.01±0.001 |

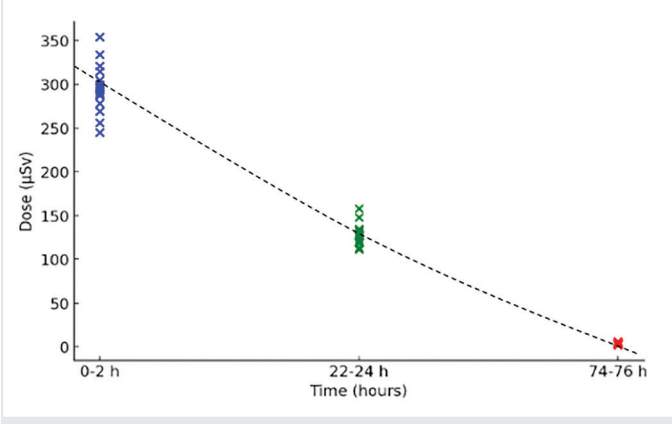


**Figure 1.** Variation in radiation exposure doses for the dentist

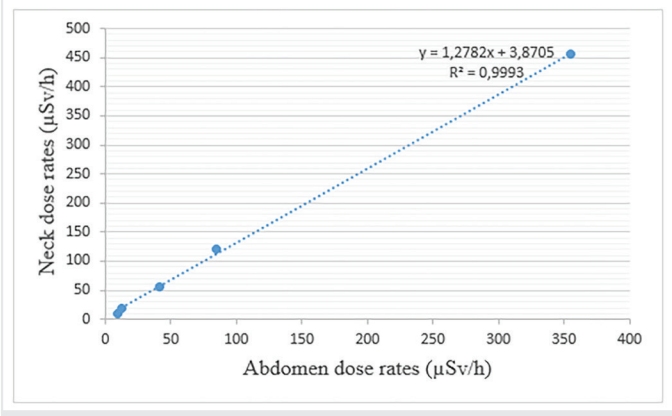


**Figure 2.** Correlation of dose rates measured from the neck and abdominal regions

### Statistical Evaluation

The differences in dose-rate measurements obtained from patients after stress and rest imaging at 10–30 minutes, 1 h, 2 h, and 3 h post-injection were evaluated using the Wilcoxon paired-sample test. The corresponding p values were 0.001, 0.01, 0.01, and 0.01, respectively, indicating statistically significant differences at all time points.

## Discussion

The activities of RAI used for thyroid carcinoma follow-up are generally not higher than those used for diagnostic purposes. However, the 364 keV gamma photons emitted by $^{131}$I are relatively high in energy, which may lead to greater radiation exposure. Since all patients had undergone total thyroidectomy prior to RAI therapy, the rapid clearance of RAI from the body can be considered advantageous. Nevertheless, when capsular invasion or distant metastases are detected, evaluation of metastatic sites may increase ambient radiation exposure. In such cases, the biological retention time of RAI increases, and therefore, radiation protection measures become even more critical. Importantly, there is no evidence in the literature suggesting that radiation emitted from RAI-treated patients leads to secondary malignancies (9).

The potential radiation exposure levels encountered by a dentist treating a thyroid cancer patient recently discharged following therapeutic RAI administration were assessed. For the general public, the daily average equivalent dose, derived from the annual public dose limit, corresponds to 2.7 μSv; dentists are classified in the same reference category in accordance with ALARA principles. Based on the measured dose rates, this study established distance and time constraints designed to ensure compliance with international radiation safety standards, keeping exposure below the annual limit of 1 mSv (1000 μSv) and the daily limit of 2.7 μSv. Compared with the annual permissible dose limit of 1 mSv, the measured doses remained within safe limits. However, given the daily dose limits, delaying dental visits for at least three days after RAI administration appears necessary. In practice, a dentist is unlikely to treat only such patients throughout the year because background radiation from natural sources, air travel, and other daily activities (e.g., X-ray screening) also contributes to cumulative radiation exposure.

In dental practice, the use of high-speed instruments such as ultrasonic scalers, air turbines, and air–water sprays generates aerosol particles containing saliva, blood, and microorganisms. Previous studies examining aerosol exposure among dental professionals have shown that clinical procedures are typically performed at approximately 30 cm from the patient, but often within a 5–60 cm range. These studies reported that aerosol exposure decreases as distance increases but increases with longer procedure duration (10). In the present study, dose-rate measurements were performed at distances of 5–30 cm, which most accurately reflect clinical conditions for dental practitioners. The measured values within this range corresponded to the highest external radiation doses, confirming that the experimental geometry effectively mimicked the true clinical scenario.

This study was designed as an experimental investigation to simulate a scenario in which a dentist performs a procedure on a patient who has undergone RAI therapy. However, in clinical practice, dentists may treat multiple patients within a year who have previously received RAI therapy. In such circumstances, it is evident that the cumulative occupational dose may exceed 1 mSv. Therefore, asking patients during the appointment scheduling process whether they have recently received RAI therapy for thyroid cancer would be beneficial from a radiation safety standpoint. Furthermore, exposure to airborne radioiodine is a potential source of contamination. Ibis et al. (11) highlighted contamination hazards associated with the release of $^{131}$I in sweat, saliva, breath, and urine following RAI therapy. The authors emphasized that because of the relatively high activity levels detected in the saliva, urine, and skin of such patients, all individuals who come into contact with them should be informed of the associated contamination risks (11). A similar consideration applies to our study, as close-range dental procedures performed on these patients may lead to increased cumulative doses through contamination. However, contamination-related dose contributions were not quantified in our study; therefore, minimizing occupational exposure remains of particular importance. Furthermore, exposure to airborne radioiodine is a potential source of contamination. Ibis et al. (11) highlighted contamination hazards associated with the release of $^{131}$I in sweat, saliva, breath, and urine following RAI therapy. The authors emphasized that, due to the relatively high activity levels found in the saliva, urine, and skin of such patients, all individuals who come into contact with them should be made aware of the associated contamination risks (12). A similar consideration applies to our study, as close-range dental procedures performed on these patients may lead to increased cumulative doses through contamination. However, contamination-related dose contributions were not quantified in our study; therefore, minimizing occupational exposure remains of particular importance.

Although no previous study has specifically investigated radiation safety for dentists working with RAI-treated patients, several reports have focused on radiation protection for family members and close contacts of such individuals. The ICRP recommends that the annual effective dose for members of the public who are not occupationally exposed to radiation should not exceed 1 mSv (6). Similarly, both the International Atomic Energy Agency and the Council Directives of the European Atomic Energy Community set the annual effective dose limit for public exposure at 1 mSv (11). The United States Nuclear Regulatory Commission has also adopted this limit, thereby reinforcing global harmonization of radiation protection standards (13).

Discharge criteria for patients receiving RAI therapy are typically based on dose-rate measurements taken at 1 meter from the patient; however, there is no universally accepted fixed threshold. The permissible dose-rate limits vary across countries — for instance, in the United States, the threshold is 70 μSv/hour, while in Türkiye the threshold is 30 μSv/hour (14,15).

The American Thyroid Association recommends that patient discharge be contingent upon the dose rate at 1 meter falling below the regulatory limit for retained $^{131}$I activity. However, while this limit may still be exceeded, adult family members and caregivers are advised to remain at least 1.8 meters from the patient; if close contact is unavoidable, interactions should be limited to a few minutes. This approach is based on the ALARA principle—"As Low As Reasonably Achievable"—which

emphasizes minimizing radiation exposure as far as practicable (16). The duration of these restrictions largely depends on factors such as the amount of residual thyroid tissue, the retained RAI activity, and the biological clearance rate of the radionuclide. Such evaluations are generally conducted in consultation with a radiation safety officer.

In thyroid cancer follow-up, two parameters are indispensable for clinical assessment: serum Tg levels and WBS. Stimulated Tg, measured under elevated TSH levels, serves as a highly sensitive biomarker for detecting residual or recurrent disease, while WBS plays a critical role in identifying the anatomical localization of residual thyroid tissue or metastatic foci (17). In this study, serum Tg levels were consistent with patients' pathological characteristics and with the administered treatment doses. Furthermore, laboratory parameters—including percentage uptake, $fT_3$, $fT_4$, and TSH—were consistent with the Society of Nuclear Medicine and Molecular Imaging Procedure Standard and European Association of Nuclear Medicine Practice Guidelines, which recommend achieving a TSH level >30 mIU/L prior to RAI administration to maximize iodine uptake. In our patient cohort, all TSH levels exceeded 60 mIU/L and were accompanied by decreased $fT_3$ and $fT_4$ values, confirming adequate thyroid stimulation and the establishment of a hypothyroid state.

This study is the first experimental, quantitative assessment of radiation doses dentists may receive during interactions with thyroid cancer patients who have recently undergone RAI WBS. The findings define practical radiation safety thresholds, including safe timing and distance parameters, for dental procedures. This evidence-based framework fills a critical knowledge gap between nuclear medicine and dental radiation protection, offering valuable guidance for maintaining safe clinical practice without delaying necessary patient care.

### Study Limitations

At the treatment clinic where this study was conducted, a radioiodine activity of 185 MBq was used for whole-body scanning in patients with thyroid cancer. However, similar studies may be performed using radioiodine activities below 185 MBq. These results may also be applied to therapeutic doses once the amount of radioiodine in the patient's body decreases below the 185 MBq threshold. The daily dose limit of 2.7 µSv used in this study was derived from the public annual dose limit of 1 mSv; practices that could lead to an increase in dose were excluded. For more detailed investigations, the sample size may be increased

## Conclusion

Dentists should inquire about patients' recent treatments to avoid exceeding dose limits. Therefore, dental interventions for these patients should be postponed until at least the second day after discharge, when radioactive decay and biological clearance sufficiently reduce external dose rates. However, when daily dose limits are taken into account, it appears necessary to delay dental visits for at least three days following RAI administration. For these patients, the allowable chairside exposure time was estimated at approximately 3.12 hours without exceeding safety limits. Nevertheless, dental procedures may be considered safe provided that the working time is kept as short as possible, procedures are performed at the greatest feasible distance from the patient, and radiation protection principles—such as the use of lead aprons and thyroid shields—are strictly followed. However, these safety recommendations do not account for potential cumulative occupational exposure that may arise when multiple treated patients are examined in rapid succession. Moreover, contamination-related exposure pathways, such as saliva, aerosols, and exhaled breath, were not quantitatively assessed. It may be recommended that pregnant dentists extend this waiting period to at least three days to comply with the more stringent annual occupational dose limit of 0.5 mSv. Overall, the findings of this study provide experimentally validated safety criteria for dentists managing patients who have recently undergone WBS with RAI. This research, By defining precise time–distance parameters between the dentist and the patient, significantly strengthens radiation protection practices and enhances interdisciplinary awareness between nuclear medicine and dental healthcare services.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the İstanbul Kent University Clinical Research Ethics Committee (approval number: 2025-07, date: 10.09.2025).

**Informed Consent:** Written informed consent was obtained from all participants prior to inclusion in the study.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - E.T.A., M.D.; Concept - M.D.; Design - E.T.A., M.D.; Data Collection or Processing - E.T.A., M.D.; Analysis or Interpretation - M.D.; Literature Search - E.T.A.; Writing - E.T.A., M.D.

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# The Predictive Value of Mesenteric and Cerebral Tissue Oxygenation Measurements for Feeding Intolerance and Necrotizing Enterocolitis in Preterm

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## ABSTRACT

**Introduction:** Necrotizing enterocolitis (NEC) is a major cause of morbidity and mortality in preterm infants. Early detection of impaired intestinal perfusion may support preventive strategies. Near-infrared spectroscopy (NIRS) is a non-invasive bedside method that continuously measures regional tissue oxygenation. This study aimed to assess whether baseline regional cerebral oxygen saturation ($rcSO_2$), regional mesenteric/splanchnic oxygen saturation ($rsSO_2$), and their ratio (SCOR), measured within the first 24–48 hours of life, could predict the development of NEC.

**Methods:** This prospective cohort study included preterm infants with gestational age <34 weeks and/or birth weight <1250 g. Infants were classified as NEC or as controls (no NEC and no feeding intolerance). Baseline $rcSO_2$ and $rsSO_2$ values were continuously recorded for one hour between 24 and 48 hours postnatal using NIRS. Demographic, maternal, and clinical data were obtained from hospital records. Appropriate parametric and non-parametric tests were used; $p<0.05$ was considered significant.

**Results:** Forty infants were included (NEC, n=18; control, n=22). Gestational age (29.27±1.64 vs. 29.50±2.18 weeks; p=0.923) and birth weight (1378.18±275.55 g vs. 1226.67±271.27 g; p=0.187) were similar between groups. Small-for-gestational-age status was observed only in the NEC group (16.7%; p=0.083). Hematocrit levels were significantly higher in the NEC group (mean ± standard deviation: 52.44±7.38% vs. 46.11±5.97%; p=0.006). Baseline $rcSO_2$ was slightly higher and $rsSO_2$ was slightly lower in infants who developed NEC, but these differences were not statistically significant ($p>0.05$). SCOR values were comparable (median= 0.7). Time to reach full enteral feeding was significantly longer in the NEC group (30.5 vs. 18.5 days; p=0.001).

**Conclusion:** Baseline cerebral and splanchnic NIRS values within the first 48 hours of life did not predict the development of NEC. Elevated hematocrit levels may indicate early circulatory vulnerability by altering microcirculation. Continuous, trend-based NIRS monitoring, in combination with clinical and biochemical parameters, may improve the prediction of NEC.

**Keywords:** Necrotizing enterocolitis, infant, premature, spectroscopy, near-infrared, splanchnic circulation, intestinal ischemia, microcirculation

## Introduction

Necrotizing enterocolitis (NEC) is one of the most devastating gastrointestinal emergencies in neonatal intensive care units (NICUs), predominantly affecting very low birth weight and preterm infants. Despite advances in neonatal care, the incidence of NEC remains between 5% and 10% among infants born before 32 weeks' gestation, with mortality rates rising to 30–50% in severe cases (1-3). Early detection of infants at risk is crucial, as clinical signs often appear only after irreversible intestinal injury has occurred.

The pathophysiology of NEC is multifactorial, including intestinal immaturity, dysbiosis, ischemia–reperfusion injury, and inflammatory responses (4,5). Among these, impaired mesenteric perfusion and oxygenation play central roles in triggering mucosal injury. Near-infrared spectroscopy (NIRS), a non-invasive tool for monitoring regional tissue oxygen saturation ($rSO_2$), provides real-time information on cerebral and mesenteric/splanchnic perfusion. Since its first clinical application by Jobsis in 1977, NIRS has been widely used in neonatal research to assess cerebral, renal, and intestinal oxygenation and has shown potential for identifying preterm infants at risk of hemodynamic instability and NEC (6-10).

Several studies have demonstrated that lower splanchnic oxygen saturation or a decreased splanchnic–cerebral oxygenation ratio (SCOR) precede NEC onset, reflecting intestinal hypoxia before clinical symptoms develop (7-12). However, findings remain inconsistent, likely

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due to methodological variability, measurement timing, and differences between NIRS devices (INVOS™ vs. NIRO™ ) (13,14). In particular, whether baseline splanchnic and cerebral oxygenation values obtained within the first two postnatal days can reliably predict NEC remains controversial. Some studies suggest that low regional splanchnic oxygen saturation ($rsSO_2$) or SCOR values in this period indicate vulnerability to intestinal ischemia, whereas others report no significant predictive association (7-12,15).

Given these uncertainties, further investigation of early NIRS measurements may clarify NIRS's role in NEC prediction and early risk stratification. Therefore, this study aimed to evaluate whether baseline splanchnic and cerebral tissue oxygenation values and their ratio (SCOR), measured within the first 24–48 hours of life using the INVOS 5100C system, were associated with the development of NEC in preterm infants.

## Methods

### Study Design and Setting

This prospective, single-center cohort study included preterm infants admitted to the tertiary-level NICU between September 2017 and August 2018. The primary objective was to assess whether baseline regional cerebral and splanchnic oxygen saturation levels, measured by NIRS during the first 24–48 hours of life, could predict the development of NEC in preterm infants. The study protocol was approved by the Local Ethics Committee of Harran University Faculty of Medicine (approval number: 08, date: 02.08.2018), and written informed consent was obtained from the parents of all participating infants.

### Study Population

Preterm infants admitted to the NICU who were <34 weeks' gestation and/or had a birth weight <1250 g were screened for eligibility. Only those who were within their first 24–48 postnatal hours and who had not yet begun enteral feeding, other than minimal trophic feeds, were considered for inclusion. Newborns were excluded if they had major congenital malformations, chromosomal abnormalities, perinatal asphyxia, hydrops fetalis, grade ≥3 intraventricular hemorrhage (IVH), hemodynamic instability, congenital heart disease affecting systemic perfusion, or were receiving inotrope or caffeine therapy.

NEC was diagnosed and staged according to the modified Bell's criteria, which combine clinical manifestations with radiologic and laboratory findings (16). Stage I included infants who presented with non-specific gastrointestinal or systemic symptoms (such as increased gastric residuals, abdominal distension, or hematochezia) without confirmatory imaging. Stages II and III were categorized as definite or advanced NEC and required radiologic evidence of intestinal involvement (pneumatosis intestinalis, portal venous air, or free intraperitoneal gas), in addition to systemic compromise (acidosis, thrombocytopenia, coagulopathy, or shock) and more pronounced abdominal signs (erythema, tenderness, or a palpable mass).

Feeding intolerance was defined as isolated gastrointestinal symptoms such as increased gastric residuals, vomiting, or abdominal distension without accompanying systemic signs or radiologic findings suggestive of NEC.

In contrast, Bell stage I NEC was diagnosed when gastrointestinal findings were accompanied by systemic signs (such as temperature instability, apnea, or lethargy) consistent with modified Bell's criteria, even in the absence of definitive radiologic findings.

Infants initially classified as having feeding intolerance were closely monitored, and those who subsequently fulfilled Bell's staging criteria were reclassified into the NEC group.

### Near-Infrared Spectroscopy Measurements

NIRS is a non-invasive bedside modality that enables continuous assessment of regional tissue oxygenation in organs such as the brain and gastrointestinal tract (6,9,10,17). The method relies on the differential absorption characteristics of oxygenated and deoxygenated hemoglobin when exposed to near-infrared light, allowing clinicians to estimate both oxygen delivery and extraction within the monitored tissue. A NIRS sensor contains a light source and two detectors positioned at different distances from the light source; the device calculates $rSO_2$ by determining the ratio of oxygenated hemoglobin to total hemoglobin. The derived $rSO_2$ signal primarily reflects venous blood (approximately 70–75%), with smaller contributions from arterial and capillary compartments (9,18).

### NIRS Monitoring Protocol

In this study, cerebral and splanchnic oxygenation values were obtained using the INVOS™ 5100C Cerebral/Somatic Oximeter (Medtronic, Minneapolis, MN, USA), an FDA-approved device widely used in neonatal monitoring (14). The infrared light emitted by the system is considered safe for continuous neonatal use and does not result in skin or tissue injury.

Before sensor placement, the skin was gently cleansed and single-use neonatal electrodes were applied to two predefined anatomical regions:

- Frontal area → regional cerebral oxygen saturation ($rcSO_2$)
- Left paraumbilical abdomen → regional splanchnic oxygen saturation ($rsSO_2$)

Measurements were recorded continuously for 1 hour between 24 and 48 hours of age. For each infant, mean, minimum, and maximum values were calculated from the recorded data. The SCOR was computed as $rsSO_2/rcSO_2$.

During the measurement period, peripheral oxygen saturation ($SpO_2$) and heart rate were monitored using a Nellcor™ bedside $SpO_2$ system, and non-invasive blood pressure was measured with a Nihon Kohden BSM-3562 monitor. No changes in respiratory support or feeding practices were made during the NIRS recording period.

### Clinical Data Collection

Demographic and perinatal variables, including gestational age, birth weight, sex, mode of delivery, small-for-gestational-age (SGA) status, and maternal comorbidities [preeclampsia, chorioamnionitis, placental pathology, and preterm premature rupture of membranes (PPROM)], were obtained from hospital records. Postnatal clinical data included Apgar scores, surfactant administration, ventilatory support (type and duration), umbilical venous catheterization (presence and

duration), hematocrit and lactate levels, history of packed red blood cell transfusion within the first 14 days, presence of hemodynamically significant patent ductus arteriosus (PDA), neonatal sepsis, IVH, timing of meconium passage, timing of initiation of minimal enteral feeding, time to reach enteral feeding volumes of 100 and 150 mL/kg/day, length of hospital stay, and survival status.

Clinical data were compared between the NEC and control groups to identify potential differences associated with NEC in clinical characteristics, risk factors, and baseline tissue oxygenation values.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean ± standard deviation for normally distributed variables, and as median (minimum–maximum) for non-normally distributed variables. Categorical variables were presented as numbers (percentages). The Shapiro–Wilk test and graphical methods were used to assess the normality of the distribution.

For group comparisons, the Student's t-test was used for normally distributed variables, while the Mann–Whitney U test was applied for non-normally distributed variables. Pearson's chi-square test or Fisher's exact test were used for categorical data as appropriate. All tests were two-tailed, and a p value <0.05 was considered statistically significant.

A post-hoc power analysis was conducted using G*Power 3.1 (Heinrich-Heine University, Düsseldorf, Germany), based on the observed difference in hematocrit levels between the NEC and control groups. With $\alpha$: 0.05 and sample sizes of 18 (NEC group) and 22 (control group), the calculated effect size (Cohen's d: 0.92) yielded a statistical power of 0.83 (83%). This indicates that the study had adequate power to detect large effect sizes in key clinical parameters.

Due to the lack of well-established effect size estimates for early baseline splanchnic NIRS measurements in preterm infants, a post-hoc power analysis based on the observed difference in hematocrit levels was performed. Therefore, the calculated power reflects the ability to detect differences in selected clinical parameters rather than in the primary NIRS-related outcomes.

## Results

During the study period, 1,704 neonates were admitted to the NICU. Of these, 40 preterm infants who met the inclusion criteria were enrolled in the study. Group 1 (control group, n=22) included infants who had no gastrointestinal symptoms or who had feeding intolerance in the absence of radiologic or systemic signs of NEC. The remaining 18 infants with confirmed Stage I, Stage II, or Stage III NEC were assigned to Group 2 (NEC group). Clinical characteristics of infants with and without NEC are detailed in Table 1.

### Demographic and Perinatal Characteristics

There were no statistically significant differences between the two groups with respect to gestational age (29.27±1.64 vs. 29.50±2.18 weeks; p=0.923), birth weight (1378.18±275.55 g vs. 1226.67±271.27 g; p=0.187), sex distribution, mode of delivery, or multiple gestations. Although all SGA infants were in the NEC group, this finding did not reach statistical significance (p=0.083). Regarding maternal characteristics, the rates of preeclampsia, chorioamnionitis, and placental disease were similar between groups. However, PPROM was significantly more common in controls than in the NEC group (27.3% vs. 0%; p=0.024). Demographic and perinatal characteristics are summarized in Table 1.

### Postnatal Clinical Findings

Postnatal clinical findings are summarized in Table 2. There were no significant differences between the groups in surfactant use, in the duration or type of mechanical ventilation (invasive or non-invasive), or in umbilical venous catheterization. The incidences of hemodynamically significant PDA, IVH, and sepsis were also similar.

Hematocrit levels at birth were significantly higher in the NEC group compared with controls (52.44±7.38% vs. 46.11±5.97%; p=0.006), whereas lactate levels did not differ significantly between groups. Packed red blood cell transfusions within the first 14 days occurred more frequently in the NEC group (27.8% vs. 4.5%), although this difference was not statistically significant (p=0.073). The median time to initiation of minimal enteral feeding was similar between groups (2 days; p=0.063). However, the time to reach full enteral feeding (150 mL/kg/day) was significantly longer in infants with NEC (median: 30.5 vs. 18.5 days; p=0.001). The median duration of hospitalization tended to be longer in the NEC group (57.5 days vs. 47 days), although the difference was not statistically significant (p=0.248). Mortality was higher in the NEC group (11.1% vs. 4.5%), but this difference was not statistically significant (p=0.579).

### Near-Infrared Spectroscopy Findings

Continuous cerebral and splanchnic NIRS monitoring was performed during the first 24–48 hours of life. In the NEC group, mean $rcSO_2$ values were calculable for 70–95% (mean 81%) of the one-hour recording period, and mean $rsSO_2$ values for 20–84% (mean 51%). In the control group, $rcSO_2$ values were available for 69–90% (mean 78.5%) and $rsSO_2$ values for 30–87% (mean 54.5%) of the measurement period.

The mean postnatal age at the time of measurement was 32.4±11.3 hours. Mean baseline $rcSO_2$ was slightly higher in the NEC group than in controls (81.83±7.99% vs. 78.55±6.60%; p=0.285), whereas mean baseline $rsSO_2$ was lower (50.11±16.80% vs. 55.60±15.41%; p=0.380). The median SCOR was 0.7 in both groups; however, the mean ratio was lower in the NEC group (0.61±0.18) than in controls (0.71±0.19), reflecting relatively impaired splanchnic oxygenation, although this difference did not reach statistical significance (p=0.143). Detailed NIRS parameters are presented in Table 3 and Figure 1.

## Discussion

In this prospective study, we found no significant association between baseline splanchnic and cerebral NIRS values or their ratio (SCOR), measured during the first 24–48 hours of life, and the subsequent development of NEC. Infants who developed NEC had significantly higher hematocrit levels at birth; SGA status and a history of packed red blood cell transfusion within the first 14 days were more frequent

**Table 1. Demographic and maternal characteristics of the study groups**

| Variable | | Group 1 (control, n=22) | Group 2 (NEC, n=18) | p value |
|---|---|---|---|---|
| Gestational age (weeks) | Min–max (median) | 27-32 (30) | 27-35 (29.5) | 0.923[a] |
| | Mean ± SD | 29.27±1.64 | 29.50±2.18 | |
| Birth weight (g) | Min–max (median) | 980-2000 (1345) | 640-1550 (1310) | 0.187[a] |
| | Mean ± SD | 1378.18±275.55 | 1226.67±271.27 | |
| Gender, n (%) | Female | 16 (72.7) | 10 (55.6) | 0.257[b] |
| | Male | 6 (27.3) | 8 (44.4) | |
| Mode of delivery, n (%) | Vaginal delivery | 4 (18.2) | 3 (16.7) | 1.000[c] |
| | Cesarean section | 18 (81.8) | 15 (83.3) | |
| Multiple gestation, n (%) | No | 12 (54.5) | 13 (72.2) | 0.251[b] |
| | Yes | 10 (45.5) | 5 (27.8) | |
| SGA, n (%) | No | 22 (100) | 15 (83.3) | 0.083[c] |
| | Yes | 0 (0) | 3 (16.7) | |
| Apgar score, 1 minute | Min–max (median) | 3-7 (5) | 0-8 (5) | 0.534[a] |
| | Mean ± SD | 5.23±1.07 | 4.89±1.64 | |
| Apgar score, 5 minute | Min–max (median) | 6-8 (6.5) | 5-9 (7) | 0.839[a] |
| | Mean ± SD | 6.64±0.73 | 6.67±1.08 | |
| Placental pathology, n (%) | No | 19 (86.4) | 14 (77.8) | 0.680[c] |
| | Yes | 3 (13.6) | 4 (22.2) | |
| Preeclampsia, n (%) | No | 19 (86.4) | 14 (77.8) | 0.680[c] |
| | Yes | 3 (13.6) | 4 (22.2) | |
| PPROM, n (%) | No | 16 (72.7) | 18 (100) | 0.024[c]* |
| | Yes | 6 (27.3) | 0 (0) | |
| Chorioamnionitis, n (%) | No | 16 (72.7) | 17 (94.4) | 0.105[c] |
| | Yes | 6 (27.3) | 1 (5.6) | |

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Fisher's exact test
*p<0.05 considered statistically significant
SGA: Small-for-gestational-age, PPROM: Preterm premature rupture of membranes, Min–max: Minimum–maximum, SD: Standard deviation, NEC: Necrotizing enterocolitis

among these infants, although these differences did not reach statistical significance. Conversely, PPROM was significantly more common in the control group, suggesting that perinatal inflammation alone may not directly predispose to NEC in this cohort.

Since Jobsis first introduced NIRS in 1977, this non-invasive tool has been widely applied to evaluate regional perfusion in neonates, including the cerebral, renal, and splanchnic circulations (6). Several studies have demonstrated decreased intestinal perfusion in conditions such as perinatal asphyxia, symptomatic anemia, hemodynamically significant PDA, and NEC (7-12,17-19). However, results regarding its predictive value for NEC remain inconsistent.

Among INVOS-based studies, Patel et al. (7) reported that $rsSO_2$ ≤56% during the first week predicted NEC, whereas Palleri et al. (11) identified $rsSO_2$ <30% between days 2–6 as strongly predictive of NEC in extremely preterm infants. In contrast, Le Bouhellec et al. (12) and Gan et al. (15) found no consistent early differences in $rcSO_2$, $rsSO_2$, or SCOR within the first 72 hours, which parallels our findings. In Gan's (15) meta-analysis of 14 studies (n=938), pooled $rsSO_2$ values were approximately 12.5% lower in infants who developed NEC; there was moderate heterogeneity, and no significant differences in cerebral oxygenation were observed. These discrepancies likely reflect the physiological nadir of intestinal oxygenation during the first two postnatal days, when mesenteric blood flow is still adapting to extrauterine life and transient decreases in $rsSO_2$ may represent normal developmental changes rather than early ischemia.

Cortez et al. (9), using the same INVOS™ 5100C system as in our study, demonstrated that in infants <30 weeks' gestation, mean mesenteric $rsSO_2$ levels began to decrease significantly after the second postnatal day, with marked drops observed after postnatal day 3 in infants with feeding intolerance and after postnatal day 5 in those who developed NEC. These findings suggest that continuous or serial monitoring beyond the first 48 hours may be more informative for detecting evolving splanchnic hypoxia. In our study, we recorded one-hour continuous baseline measurements between 24 and 48 hours, offering more stable averages than the short 5-minute recordings used in some prior studies (7,10,19). However, no significant predictive thresholds emerged.

Previous studies have identified several risk factors associated with NEC, including low birth weight, SGA status, and high hematocrit levels; these factors may contribute to reduced mesenteric flow and microcirculatory impairment (20,21). Dani et al. (20) reported that SGA infants exhibited lower $rsSO_2$ values than appropriate-for-gestational-age peers regardless of feeding status, likely reflecting chronic intrauterine hypoperfusion.

**Table 2. Postnatal clinical characteristics of the study groups**

| Variable | | Control group (n=22) | NEC group (n=18) | p value |
|---|---|---|---|---|
| **Surfactant therapy, n (%)** | No | 2 (9.1) | 2 (11.1) | 1.000[c] |
| | Yes | 20 (90.9) | 16 (88.9) | |
| **Invasive ventilation, n (%)** | No | 11 (50.0) | 5 (27.8) | 0.154[b] |
| | Yes | 11 (50.0) | 13 (72.2) | |
| **Duration of invasive ventilation (days)** | Min–max (median) | 1-18 (4) | 2-13 (3) | 0.768[a] |
| | Mean ± SD | 6.00±5.93 | 5.00±3.70 | |
| **Non-invasive ventilation, n (%)** | No | 1 (4.5) | 1 (5.6) | 1.000[c] |
| | Yes | 21 (95.5) | 17 (94.4) | |
| **Duration of non-invasive ventilation (days)** | Min–max (median) | 1-83 (8.5) | 1-39 (16) | 0.428[a] |
| | Mean ± SD | 15.22±20.24 | 14.47±10.79 | |
| **Hemodynamically significant PDA, n (%)** | No | 14 (63.6) | 8 (44.4) | 0.225[b] |
| | Yes | 8 (36.4) | 10 (55.6) | |
| **IVH, n (%)** | No | 15 (68.2) | 13 (72.2) | 0.781[b] |
| | Yes | 7 (31.8) | 5 (27.8) | |
| **Sepsis, n (%)** | No | 4 (18.2) | 0 (0) | 0.114[c] |
| | Yes | 18 (81.8) | 18 (100) | |
| **Umbilical venous catheter, n (%)** | No | 3 (13.6) | 2 (11.1) | 1.000[c] |
| | Yes | 19 (86.4) | 16 (88.9) | |
| **Duration of umbilical venous catheter (days)** | Min–max (median) | 3-18 (9.5) | 3-19 (13) | 0.312[a] |
| | Mean ± SD | 9.44±4.76 | 11.27±5.11 | |
| **Hematocrit at birth (%)** | Min–max (median) | 37-58.1 (45.5) | 40.4-67.5 (53.5) | 0.006[a]** |
| | Mean ± SD | 46.11±5.97 | 52.44±7.38 | |
| **Lactate (mmoL/L)** | Min–max (median) | 1.5-9.1 (2.8) | 1.3-17 (3) | 0.549[a] |
| | Mean ± SD | 3.47±1.94 | 4.73±4.19 | |
| **RBC transfusion within first 14 days, n (%)** | No | 21 (95.5) | 13 (72.2) | 0.073[c] |
| | Yes | 1 (4.5) | 5 (27.8) | |
| **First meconium passage, n (%)** | Within 24 h | 11 (50.0) | 10 (55.6) | 0.726[b] |
| | After 24 h | 11 (50.0) | 8 (44.4) | |
| **Time to minimal enteral feeding (days)** | Min–max (median) | 1-6 (2) | 1-5 (2) | 0.063[a] |
| | Mean ± SD | 2.79±1.47 | 2.00±1.03 | |
| **Time to enteral feeding (100 mL/kg/day) (days)** | Min–max (median) | 7-31 (12) | 12-47 (26.5) | 0.001[a]** |
| | Mean ± SD | 14.83±6.33 | 26.75±8.99 | |
| **Time to full enteral feeding (150 mL/kg/day) (days)** | Min–max (median) | 10-36 (18.5) | 18-50 (30.5) | 0.001[a]** |
| | Mean ± SD | 19.67±7.04 | 32.25±9.29 | |
| **Length of hospital stay (days)** | Min–max (median) | 10-111 (47) | 10-206 (57.5) | 0.248[a] |
| | Mean ± SD | 50.63±23.55 | 64.44±43.52 | |
| **Outcome, n (%)**<br>**Mortality, n (%)** | Survived | 21 (95.5) | 16 (88.9) | 0.579[c] |
| | Died | 1 (4.5) | 2 (11.1) | |

[a]Mann-Whitney U test, [b]Pearson chi-square test, [c]Fisher's exact test
**p<0.01 was considered statistically significant
PDA: Patent ductus arteriosus, IVH: Intraventricular hemorrhage, RBC: Red blood cell, Min–max: Minimum–maximum, SD: Standard deviation, NEC: Necrotizing enterocolitis

Similarly, in our cohort, SGA status and higher hematocrit levels were more frequent in the NEC group, although the differences did not reach statistical significance, supporting the hypothesis that increased blood viscosity and impaired oxygen delivery may contribute to intestinal ischemia in vulnerable preterm infants.

The significantly higher hematocrit levels observed in the NEC group deserve particular consideration when interpreting splanchnic NIRS measurements. Elevated hematocrit may influence regional oxygen saturation readings through two mechanisms: increased blood viscosity leading to true microcirculatory hypoperfusion, and increased optical density affecting near-infrared light absorption. Both mechanisms may artificially lower $rsSO_2$ values, and therefore represent potential confounders in the interpretation of NIRS-derived splanchnic oxygenation.

**Table 3. Comparison of baseline NIRS measurements between groups**

| Variable | | Group 1 (control, n=22) | Group 2 (NEC, n=18) | p value |
|---|---|---|---|---|
| Baseline cerebral $rcSO_2$ | Min–max (median) | 69-90 (78.5) | 70-95 (81) | [a]0.285 |
| | Mean ± SD | 78.55±6.60 | 81.83±7.99 | |
| Baseline splanchnic $rSO_2$ | Min–max (median) | 30-87 (54.5) | 20-84 (51) | [a]0.380 |
| | Mean ± SD | 55.60±15.41 | 50.11±16.80 | |
| Baseline splanchnic/cerebral oxygenation ratio (SCOR) | Min–max (median) | 0.4-1 (0.7) | 0.3-0.9 (0.7) | [a]0.143 |
| | Mean ± SD | 0.71±0.19 | 0.61±0.18 | |

[a]Mann-Whitney U test
NIRS: Near-infrared spectroscopy, Min–max: Minimum–maximum, SD: Standard deviation, $rcSO_2$: Regional cerebral oxygen saturation, $rSO_2$: Regional oxygen saturation

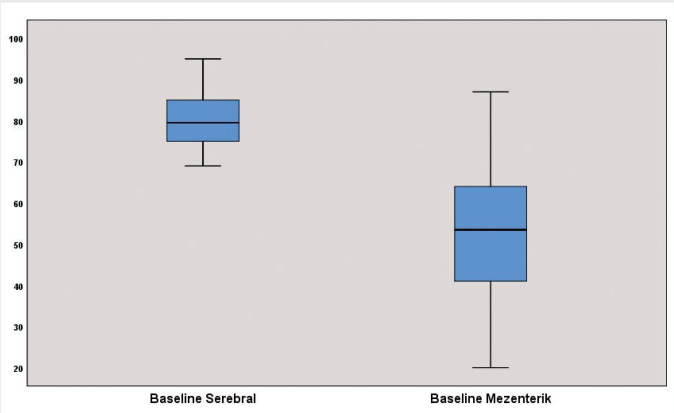


**Figure 1.** Distribution of baseline cerebral and baseline mesenteric NIRS measurements
NIRS: Near-infrared spectroscopy

Patel et al. (7) showed that preterm infants who later developed NEC had lower $rsSO_2$ both during the first 48 hours and throughout the first week of life. Their $rsSO_2$ levels were lowest on day 1 (73.8±1.8%) and increased by day 3 to 80.0±1.4% (7). In our cohort, the proportion of infants with $rsSO_2$ <56% was 61.1% in the NEC group and 50% in controls, suggesting a similar trend that was not statistically significant, possibly due to the small sample size and a narrower measurement window. Notably, Patel et al. (7) NEC infants had lower gestational ages and birth weights, whereas our groups were matched for both parameters; this matching may have reduced confounding related to maturity.

Schat et al. (19) demonstrated that differences between mesenteric and cerebral oxygenation (SCOR) were associated with intestinal perforation and mortality, highlighting the value of combined indices. Fortune et al. (8) reported lower SCOR ratios in NEC, and SCOR <0.75 showing the highest predictive accuracy for splanchnic ischemia. Although our mean SCOR values were numerically lower in the NEC group (0.61±0.18 vs. 0.71±0.19), this difference did not reach statistical significance, which likely reflects the very early timing of measurement—before the onset of substantial regional perfusion imbalance.

While some authors have reported that low baseline mesenteric oxygenation predicts NEC (8,22), others—consistent with our results—have found no clear predictive relationship, suggesting that static baseline measurements may be less informative than dynamic trends. Serial or continuous NIRS monitoring, rather than a single early measurement, may better capture the evolving hemodynamic changes preceding NEC onset (17).

Nutritional and circulatory factors also play critical roles in NEC pathogenesis. Inadequate fetal and early postnatal nutrition is associated with long-term adverse outcomes such as cardiovascular and metabolic diseases and neurodevelopmental impairment (1,4,5). Early initiation of enteral nutrition and balanced advancement of feeds reduce the risk of infection, catheter-related complications, and length of hospital stay (1,14). The prolonged time required to achieve full enteral feeding in infants with NEC should be interpreted as an outcome of the disease and its management, as enteral feeding is routinely interrupted during NEC episodes, rather than as a predictive or predisposing factor.

### Study Limitations

This study has several limitations. The sample size was relatively small, and the study was conducted at a single center, which may limit generalizability and reduce statistical power to detect subtle differences. The one-hour baseline monitoring period, although longer than in some previous studies, may still have missed transient perfusion fluctuations. Additionally, hemodynamically unstable infants were excluded, potentially underrepresenting those at greatest risk for NEC. Device- and operator-related artifacts may also have influenced NIRS measurements.

An additional limitation was the relatively low signal availability of splanchnic NIRS measurements, with approximately 50% of the recording period yielding usable $rsSO_2$ data. This reflects known technical challenges of abdominal NIRS monitoring in preterm infants, including motion artifacts, bowel gas, and probe displacement, which may have affected the reliability of mean splanchnic oxygenation values.

## Conclusion

Baseline splanchnic and cerebral tissue oxygenation values and SCOR ratios, measured during the first 24–48 hours of life using the INVOS™ 5100C system, did not predict the development of NEC in preterm infants. Although early static measurements appear insufficient for reliable risk prediction, combining continuous, trend-based NIRS monitoring with clinical indicators and biochemical markers may improve early identification of splanchnic hypoxia and guide preventive strategies. Future research should focus on continuous, trend-based monitoring and integration of NIRS data with clinical and biochemical markers to refine NEC risk prediction and improve neonatal outcomes.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Local Ethics Committee of Harran University Faculty of Medicine (approval number: 08, date: 02.08.2018).

**Informed Consent:** The written informed consent was obtained from the parents of all participating infants.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - M.B., Ö.İ.; Concept - M.B., Ö.İ.; Design - M.B., Ö.İ.; Data Collection or Processing - M.B., Ö.İ.; Analysis or Interpretation - M.B.; Literature Search - M.B.; Writing - M.B.

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# The Effect of Chronic Diseases on Sleep Quality: A Single-Center Study from a Family Medicine Perspective

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## ABSTRACT

**Introduction:** This cross-sectional study aimed to evaluate the prevalence of poor sleep quality and determine the specific impact of the number, type, and comorbidity (multimorbidity) of chronic diseases on sleep quality among individuals followed in primary care.

**Methods:** This descriptive study, conducted at a family health center in İstanbul, Türkiye, between June and August 2024, included 268 adult patients diagnosed with at least one chronic disease. Data were collected using a sociodemographic and clinical data form and the Pittsburgh Sleep Quality Index (PSQI). Statistical analyses were performed using descriptive statistics and the Mann-Whitney U, Kruskal-Wallis, and Spearman's correlation tests; the significance level was set at $p<0.05$.

**Results:** Participants' mean age was 54.29±17.1 years; 52.6% were female. The mean number of chronic diseases per person was 2.62. The most prevalent diseases were hypertension (36.57%), diabetes mellitus (22.01%), and vitamin D deficiency (17.91%). Poor sleep quality (PSQI ≥5) was identified in a high proportion of participants (59.3; n=159). A significant positive correlation was found between the number of chronic diseases (multimorbidity) and the total PSQI score (r: 0.227, $p<0.001$). Total PSQI scores were significantly higher in individuals with psychiatric diseases ($p=0.029$), COPD ($p=0.003$), migraine ($p=0.004$), and skin diseases ($p=0.002$). Furthermore, disease clusters, notably the comorbidity of hypertension and diabetes and the combination of vitamin D and B12 deficiencies, exerted a more detrimental effect on sleep quality and daytime functioning than isolated diseases.

**Conclusion:** Sleep disturbances are highly prevalent in primary care patients with chronic conditions. Multimorbidity has been confirmed as an independent risk factor for impaired sleep quality, particularly when it involves psychiatric, respiratory, neurological, and metabolic conditions. Family physicians should prioritize routine sleep quality screening in chronic disease management and integrate personalized, holistic interventions.

**Keywords:** Family practice, chronic disease, sleep quality, Pittsburgh Sleep Quality Index, multimorbidity

## Introduction

Chronic diseases are leading causes of morbidity and mortality in modern societies and have a profound impact on individuals' quality of life. The management of chronic diseases accounts for a significant proportion of primary healthcare visits in Türkiye and globally (1). These diseases adversely affect physical functioning, psychological health, and social well-being.

Sleep is a fundamental process essential for physiological and psychological restoration. Optimal sleep quality is a crucial indicator of overall health and quality of life (2). A bidirectional, complex relationship exists between chronic diseases and sleep disorders. While symptoms such as pain, dyspnea (shortness of breath), and nocturia interrupt sleep, insufficient sleep can worsen the course of chronic diseases by lowering the pain threshold, increasing the inflammatory response, and disrupting metabolic balance (3).

Family physicians, given their role in providing long-term, comprehensive care that addresses individuals holistically, are ideally placed to diagnose sleep problems early and manage sleep problems in individuals with chronic diseases. The aim of this study is to assess sleep quality in individuals with one or more chronic diseases who present to a family medicine unit and to determine the relationship between sleep quality and specific chronic diseases and multimorbidity.

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## Methods

### Study Design and Setting

This cross-sectional descriptive study was conducted between June and August 2024 at a family health center in İstanbul, Türkiye.

### Study Population and Sampling Strategy

The study population comprised 804 individuals registered at family medicine unit number: 89 who had been diagnosed with at least one chronic disease. A consecutive sampling method was employed to minimize selection bias. All patients presenting to the clinic during the study period who met the inclusion criteria were invited to participate. Among the target population, 280 individuals agreed to participate. Twelve participants were subsequently excluded due to incomplete data or withdrawal, resulting in a final sample size of 268. The participation rate was approximately 33.3% of the total registered population with chronic disease, thereby providing a representative sample for the unit. A post-hoc power analysis indicated that the sample size of 268 was sufficient to achieve >80% power and to estimate the primary outcome measures with 95% confidence intervals.

### Inclusion and Exclusion Criteria

The inclusion criteria were being registered at the specific family medicine unit, being 18 years of age or older, having at least one diagnosed chronic disease, and voluntarily agreeing to participate. The exclusion criteria were defined as: not being registered at the center; the absence of any chronic disease; the presence of an acute severe illness requiring urgent intervention; or cognitive impairment preventing effective communication and data collection.

### Rationale for Vitamin D Evaluation

In this study, vitamin D deficiency was evaluated within the category of chronic diseases. Although often classified as a nutritional deficiency, it was included in the chronic disease spectrum because of its high prevalence in primary care, the need for long-term monitoring and replacement therapy, and its established role in the etiology and progression of various chronic conditions, including metabolic and musculoskeletal disorders.

### Data Collection Instruments

• Sociodemographic and clinical data form: This form, prepared by the researchers, was used to collect information on age, gender, education, income, body mass index (BMI), and current chronic disease diagnoses (based on patient self-report and/or medical records).

• The Pittsburgh Sleep Quality Index (PSQI), which has demonstrated high validity and reliability, was used to evaluate sleep quality. A global score of 5 or greater indicates poor sleep quality.

### Ethical Approval

The study received ethical approval from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 282, date: 14.03.2024). Written informed consent was obtained from all participants.

### Statistical Analysis

Data were analyzed using SPSS 27.0 version (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, frequency) were calculated. Normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Non-parametric tests (Mann-Whitney U, Kruskal-Wallis, Spearman correlation) were used for data that did not meet the assumption of normality. The level of statistical significance was set at $p<0.05$.

## Results

The participants were predominantly female (52.6%), with a mean age of 54.3±17.1 years. The mean BMI was 26.5±4.8 kg/m², falling into the overweight range. The sociodemographic characteristics of the participants are summarized in Table 1.

The mean number of chronic diseases per person was 2.62. The prevalence of the identified chronic diseases is presented in Table 2. The most common conditions were hypertension, diabetes mellitus, and vitamin D deficiency.

The participants' mean global PSQI score was 6.09±3.61. A total of 159 participants (59.3%) were classified as having poor sleep quality (PSQI score ≥5). Total PSQI scores increased significantly with the number of chronic diseases (r: 0.227, $p<0.001$).

When sleep quality was compared according to sociodemographic variables (Table 3), women had significantly higher scores than men for specific sub-domains such as sleep latency ($p=0.006$) and use of sleep medication ($p=0.020$), although the difference in global PSQI was not statistically significant ($p=0.060$). Additionally, participants who

**Table 1. Sociodemographic characteristics of the participants (n=268)**

| Variable | Category | n | % |
|---|---|---|---|
| Gender | Female | 141 | 52.6 |
| | Male | 127 | 47.4 |
| Marital status | Married | 182 | 67.9 |
| | Single/divorced/widowed | 86 | 32.1 |
| Education level | Primary school or below | 101 | 37.6 |
| | High school | 78 | 29.1 |
| | University/higher education | 89 | 33.1 |
| Employment status | Employed | 108 | 40.3 |
| | Unemployed/retired/housewife | 160 | 59.7 |
| Housing status | Homeowner | 183 | 68.3 |
| | Tenant (renting) | 75 | 28.0 |
| BMI category | Normal weight | 105 | 39.2 |
| | Overweight | 97 | 36.2 |
| | Obese | 59 | 22.0 |
| | Underweight | 7 | 2.6 |
| Quantitative data | | Mean | SD |
| Age (years) | | 54.29 | 17.1 |
| BMI (kg/m²) | | 26.5 | 4.8 |
| Number of chronic diseases | | 2.62 | - |

BMI: Body mass index, SD: Standard deviation

were tenants had significantly higher sleep disturbance scores than homeowners (p=0.011).

Comparison of global PSQI scores across specific disease groups revealed that individuals with psychiatric disorders, COPD, migraine, and skin diseases had significantly poorer sleep quality than those without these conditions (Table 4).

The analysis of disease multimorbidity revealed that the coexistence of hypertension and diabetes was associated with a significantly worse total PSQI score, with a mean of 6.45±4.06, compared with those without this combination (p=0.017). Similarly, the combination of vitamin D and vitamin B12 deficiencies was associated with significantly higher sleep disturbance scores (p=0.027).

## Discussion

This cross-sectional study revealed that sleep disturbances were highly prevalent (59.3%) among individuals with chronic diseases followed in primary care, and demonstrated that sleep quality was significantly associated with multimorbidity. Our findings support the necessity of addressing sleep health as a central component in chronic disease management.

**Table 2. Prevalence of chronic diseases in the study population**

| Chronic disease | n | % |
|---|---|---|
| Hypertension | 98 | 36.57 |
| Diabetes mellitus | 59 | 22.01 |
| Vitamin D deficiency | 48 | 17.91 |
| Cardiovascular diseases | 43 | 16.04 |
| Hyperlipidemia | 42 | 15.67 |
| Vitamin B12 deficiency | 41 | 15.30 |
| Allergy | 35 | 13.06 |
| Thyroid disorders (hypothyroid) | 26 | 9.70 |
| Anemia | 25 | 9.33 |
| Gastroesophageal reflux disease | 23 | 8.58 |
| Migraine | 18 | 6.72 |
| Psychiatric disorders | 17 | 6.34 |
| Skin diseases | 17 | 6.34 |
| COPD | 11 | 4.10 |

COPD: Chronic obstructive pulmonary disease

One of the most striking findings of our research is a linear deterioration in sleep quality with an increasing number of chronic diseases (multimorbidity) (r: 0.227, p<0.001). This suggests that various pathophysiological mechanisms (inflammation, pain, medication side effects, and psychosocial stress) converge synergistically to disrupt sleep architecture. The literature indicates that multiple chronic conditions impair sleep architecture through increased systemic inflammation, thereby creating a vicious cycle that promotes disease progression (4). Our study confirms this pronounced relationship within the primary care patient population.

The high PSQI scores observed in individuals with psychiatric disorders indicate that this group is particularly vulnerable to sleep disturbances. This finding is consistent with evidence that depression and anxiety profoundly affect the sleep-wake cycle through hyperarousal and circadian rhythm disturbances (5). Furthermore, the significantly higher use of sleep medications in this group reflects the need for pharmacological management of psychiatric symptoms and serves as a reminder to exercise caution regarding long-term use (6).

The higher sleep latency and use of sleep medication among women align with established gender-specific sleep differences in the literature. Jaussent et al. (7) reported increased use of hypnotic medication in women during the menopausal transition, suggesting a link to hormonal fluctuations. Additionally, social roles and the higher prevalence of anxiety among women may contribute to difficulties initiating sleep (8). Conversely, the shorter sleep latency observed in individuals with very high income (p=0.048) may indicate that economic security reduces the physiological stress response, thereby facilitating sleep onset (9).

The negative impact of metabolic disease clustering (hypertension, diabetes, hyperlipidemia) on sleep quality was clearly evident in our study. Specifically, the coexistence of hypertension and diabetes significantly worsened the total PSQI score, sleep disturbance, and daytime dysfunction. This can be explained by insulin resistance and hyperglycemia disrupting the circadian rhythm (10), and hypertension is strongly associated with sleep apnea and fragmented sleep (11). These effects appear to be exacerbated when combined.

The high sleep latency and impaired sleep quality observed in individuals with COPD are consistent with sleep fragmentation caused by dyspnea and hypoxemia (5). Similarly, severe sleep disturbances in

**Table 3. Global PSQI scores and significant sub-domain findings by sociodemographic variables**

| Variable | Category | Global PSQI (mean ± SD) | p | Significant sub-domain findings |
|---|---|---|---|---|
| Gender | Female | 6.49±3.78 | 0.060 | Sleep latency: Higher in females (p=0.006*)<br>Medication use: Higher in females (p=0.020*) |
| | Male | 5.65±3.37 | | |
| Housing status | Homeowner | 5.90±3.45 | 0.193 | Sleep disturbance: Higher in tenants (p=0.011*) |
| | Tenant | 6.67±3.97 | | |
| Employment status | Employed | 5.84±2.98 | 0.830 | Sleep efficiency: Better in employed (p=0.044*) |
| | Unemployed/ retired/housewife | 6.26±3.97 | | |

Mann-Whitney U test. p<0.05 is considered significant.*
PSQI: Pittsburgh Sleep Quality Index, SD: Standard deviation

**Table 4. Comparison of Global PSQI scores between patients with and without specific chronic diseases**

| Disease | Status | n | Global PSQI (mean ± SD) | p |
|---|---|---|---|---|
| Psychiatric illness | Present | 17 | 8.71±5.50 | 0.029* |
| | Absent | 251 | 5.92±3.39 | |
| COPD | Present | 11 | 8.62±4.42 | 0.003* |
| | Absent | 257 | 6.90±2.48 | |
| Migraine | Present | 18 | 8.72±4.32 | 0.004* |
| | Absent | 250 | 5.90±3.48 | |
| Skin diseases | Present | 17 | 8.82±4.30 | 0.002* |
| | Absent | 251 | 5.91±3.49 | |
| Diabetes mellitus | Present | 59 | 7.35±3.85 | 0.031* |
| | Absent | 209 | 5.93±3.55 | |
| Hypertension | Present | 98 | 6.15±3.93 | 0.810 |
| | Absent | 170 | 6.06±3.42 | |

*Mann-Whitney U test. Statistically significant ($p<0.05$). COPD: Chronic obstructive pulmonary disease, PSQI: Pittsburgh Sleep Quality Index, SD: Standard deviation

individuals with migraine and in those with skin disease are linked to the sleep-disrupting nature of pain (12) and of intractable pruritus (13), respectively.

The strong negative effect of the coexistence of vitamin D and B12 deficiencies on sleep quality is noteworthy. Vitamin B12 contributes to methionine synthesis, which is involved in melatonin synthesis; its deficiency is associated with neuropathic pain and restless legs syndrome (14,15). The co-occurrence of these deficiencies is likely to contribute to impaired sleep through overlapping neurobiological and metabolic pathways; however, this hypothesis requires confirmation in mechanistic studies.

The impact of socioeconomic factors on sleep was further confirmed by higher sleep disturbance scores in tenants ($p=0.011$). Balaban et al. (16) reported that housing insecurity and financial stress are associated with increased sleep fragmentation and latency.

### Study Limitations

The results of this study do not permit causal inference because of its cross-sectional design. The reliance on self-reported data introduces the risk of recall bias. Being conducted at a single center may limit the generalizability of the findings.

## Conclusion

Sleep disturbances are highly prevalent among individuals with chronic diseases, and multimorbidity further exacerbates this risk. Psychiatric, respiratory and neurological diseases, as well as components of metabolic syndrome, have a pronounced negative impact on sleep quality. It is of paramount importance to integrate personalized interventions aimed at assessing and improving sleep health into chronic disease management within primary healthcare services.

### Ethics

**Ethics Committee Approval:** The study received ethical approval from the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (decision number: 282, date: 14.03.2024).

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

### Footnotes

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

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

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# Clinical Outcomes of Stage IS Non-seminomatous Germ Cell Testicular Tumors: Single-Center Experience

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## ABSTRACT

**Introduction:** Stage IS non-seminomatous germ cell tumors (NSGCT) represent a rare and clinically heterogeneous subgroup characterised by persistent postoperative elevation of serum tumor markers despite the absence of radiological metastasis. Evidence guiding optimal management remains limited because most studies address this population only as part of broader stage I cohorts. To evaluate the clinical characteristics, treatment strategies, tumor marker dynamics, and long-term oncological outcomes of patients with stage IS NSGCT managed at a single tertiary centre.

**Methods:** This retrospective observational study included 25 patients diagnosed with stage IS NSGCT between 2008 and 2022. All patients demonstrated persistently elevated serum alpha-fetoprotein, beta-human chorionic gonadotropin, or lactate dehydrogenase following orchiectomy, with no radiological evidence of metastasis. Demographic, pathological, and treatment data were analysed. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan–Meier approach, and potential predictors of DFS were assessed through a univariate Cox regression model.

**Results:** The median patient age was 26 years; mixed germ cell tumor histology accounted for 80% of cases. After orchiectomy, all patients received bleomycin, etoposide, and cisplatin chemotherapy; receiving ≥3 cycles significantly reduced the risk of recurrence [hazard ratios (HR): 0.075, p=0.026)]. Rete testis invasion was associated with a trend toward an increased risk of relapse, although this did not reach statistical significance (HR: 8.389, p=0.066). At a median follow-up of 155.5 months, the 10-year relapse incidence was 16%, and median DFS and OS were not reached.

**Conclusion:** Stage IS NSGCT carries a substantial risk of occult metastatic disease despite negative imaging, supporting the need for systemic therapy in most cases. Adequate chemotherapy intensity appears crucial for long-term disease control. Although certain pathological features—such as rete testis invasion—may indicate more aggressive biology, their prognostic relevance requires confirmation in larger, prospective cohorts.

**Keywords:** Stage IS NSGCT, testicular cancer, tumor markers, BEP chemotherapy

## Introduction

Even though testicular tumors account for only 1% of all solid malignancies in men, they constitute the most common solid malignancy among men aged 15–35 years (1). Testicular tumors are classified as solid malignancies in men and are broadly divided into two main categories: germ cell tumors and sex cord–stromal tumors. Approximately 95% of these cases are germ cell tumors, which are further classified into pure seminomas and non-seminomatous germ cell tumors (NSGCTs). NSGCT may consist of one or more of the following components: embryonal carcinoma, yolk sac tumor, teratoma, and choriocarcinoma (2).

Approximately 60% of NSGCTs are classified as stage I disease at initial presentation (3). Stage IS NSGCT is characterised by elevated tumor markers after orchiectomy, despite the disease being confined to the testicle. Elevated tumor markers were defined using threshold values of >15 ng/mL for alpha-fetoprotein (AFP), >5 U/L for beta-human chorionic gonadotropin (β-hCG), and >200 U/L for lactate dehydrogenase (LDH), and biological half-lives of AFP (5–7 days) and β-hCG (24–36 hours) were considered during evaluation. This group has a favourable prognosis in metastatic patients, but exhibits heterogeneity in stage and tumor burden. This heterogeneity is reflected in clinical practice by variations in the rate of tumor marker decline following orchiectomy, as well as by differences in histological subtypes, which variably influence clinical course and treatment requirements. Despite normal radiological findings, persistent elevation of serum tumor markers is the only indication of disease persistence. Close monitoring is often preferred for patients who

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show a downward trend in tumor markers after orchiectomy and in whom imaging detects no metastases. This approach allows patients to be monitored until tumor markers reach the lowest levels, revealing that a significant proportion of cases are stage IA or IB. This prevents unnecessary early initiation of chemotherapy and overtreatment. However, in patients whose marker levels remain markedly elevated or continue to rise after orchiectomy, the likelihood of metastatic disease is high. Therefore, this subgroup should be treated with the chemotherapy protocols used for advanced or metastatic NSGCT patients (4).

Consequently, stage IS NSGCT represents a subgroup with high clinical uncertainty. Furthermore, limited data in the literature for this patient group and the fact that most existing studies evaluate stage IS patients as a small subgroup within large stage I cohorts perpetuate uncertainty regarding the optimal timing of treatment strategies and long-term outcomes. In the management of this disease, which particularly affects the younger age group, both oncological outcomes and long-term morbidity are of great importance. The objective of this study is to retrospectively analyze the clinical features, tumor marker behavior, treatment strategies, and long-term oncological outcomes of patients with stage IS NSGCT managed at our center. Our hypothesis is that administration of three or more cycles of chemotherapy is associated with improved disease-free survival (DFS). By doing so, we aim to enhance the current understanding of this uncommon patient population and support the refinement of clinical decision-making in their care.

## Methods

### Study Design and Patient Selection

This retrospective, observational, single-center study analyzed patients with stage IS NSGCT who were diagnosed and followed at a tertiary oncology center between 2008 and 2022. The diagnosis of stage IS was based on persistently elevated serum tumor marker levels (AFP, β-hCG, and LDH) in the absence of metastatic disease on imaging after orchiectomy.

The inclusion criteria for the study were histopathologically confirmed diagnosis of NSGCT, prior orchiectomy, persistently elevated serum tumor markers in the postoperative period, and no evidence of metastatic disease on computed tomography scans of the thorax, abdomen, and pelvis. Furthermore, the availability of complete patient follow-up data is required for inclusion.

In histopathological evaluation, the presence of an embryonal carcinoma component constituting more than 30% of the tumor is considered indicative of embryonal carcinoma predominance.

Patients were classified into good- and intermediate-risk groups according to the IGCCCG prognostic classification based on the primary tumor site, presence of visceral metastases, and serum AFP, β-hCG, and LDH levels (5). Although the IGCCCG classification was originally developed for metastatic germ cell tumors, it was applied in the present study to provide a prognostic framework for stage IS patients with persistently elevated tumor markers, reflecting potential occult systemic disease.

Ethical approval for this study was obtained from Kartal Dr. Lütfi Kırdar City Hospital, Scientific Research Ethics Committee (approval number: 2025/010.99/21/9, date: 30.10.2025), and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

### Data Collection

Information regarding patients' demographic characteristics; tumor histology and location; tumor marker levels; pathological T stage; radiological imaging findings; treatment regimens; recurrence and development of metastatic disease; dates of death and recurrence and of recurrence; and the entire follow-up process was obtained through review of the hospital's electronic archive system, patient files, and clinical records.

### Treatment Strategies

In the study, all patients received the standard bleomycin, etoposide, and cisplatin (BEP) chemotherapy regimen as systemic treatment. Bleomycin was administered at a total dose of 30 mg intravenously on days 2, 9, and 16 of each treatment cycle. Etoposide was given as a daily intravenous infusion at 100 mg/m² from days 1 to 5 of each cycle, and cisplatin was administered as a daily intravenous infusion at 20 mg/m² during the same period. The number of treatments administered varied according to the patient's clinical condition and was recorded separately for each patient.

### Study Endpoints

The primary outcome measure of this study was DFS. DFS was defined as the time from completion of treatment following surgery until the first recurrence or progression; overall survival (OS) was defined as the time from surgery until death from any cause.

### Follow-up Protocol

After treatment, all patients were followed according to a standard follow-up protocol consistent with the National Comprehensive Cancer Network guidelines (6). During the first year, patients underwent physical examinations every two months and serum tumor markers were assessed. During the same period, abdominopelvic computed tomography and chest X-rays were repeated every 4 to 6 months. In the second year, physical examinations and tumor markers were monitored every three months; abdominopelvic imaging and chest X-rays were performed at 6- to 12-month intervals. In the third year, patients underwent physical examinations and tumor marker measurements every 3–6 months, and abdominopelvic imaging was performed annually. In the fourth and fifth years, physical examinations and tumor-marker assessments were performed every six months; radiological investigations were conducted as clinically indicated. If any suspicion of recurrence arises during this process, patient follow-up is intensified with additional imaging modalities and appropriate clinical assessments.

### Statistical Analysis

All statistical procedures were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as median values with their ranges

(minimum–maximum), whereas categorical variables were presented as frequencies and percentages. Survival probabilities for DFS and OS were estimated using the Kaplan–Meier method. Potential prognostic variables considered to influence DFS were examined using univariate Cox regression analysis. Outcomes from the univariate Cox models were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) and corresponding p values. A two-sided p value <0.05 was considered statistically significant. Because of the limited numbers of patients and events, a multivariate Cox regression model could not be performed.

## Results

### Patient Baseline Characteristics

A total of 25 patients were evaluated in this study. The median age was 26 years (range: 17–36 years), and the demographic and clinical features of the cohort are presented in Table 1. In terms of primary tumor stage, 12 patients (48%) were classified as T1 and 13 (52%) as T2. Rete testis invasion was present in 7 (28%) patients.

The most common subtype identified on histological evaluation was the mixed germ-cell tumor, detected in 20 patients (80%). Embryonal carcinoma was observed in 4 patients (16%), and yolk sac tumor was observed in 1 patient (4%). Tumor localisation was right-sided in 14 patients (56%) and left-sided in 11 patients (44%).

**Table 1. Clinical and pathological characteristics of the patients**

| Characteristics | n, (%) |
|---|---|
| Age<br>Median<br>Range (minimum-maximum) | <br>26 (17-36) |
| Extent of primary tumor<br>T1<br>T2 | <br>12 (48%)<br>13 (52%) |
| Rete testis invasion<br>Absent<br>Present | <br>18 (72%)<br>7 (28%) |
| Histology<br>Mixed germ cell tumor<br>Embryonal carcinoma<br>Yolk sac tumor | <br>20 (80%)<br>4 (16%)<br>1 (4%) |
| Tumor location<br>Right<br>Left | <br>14 (56%)<br>11 (44%) |
| AFP (ng/mL)<br>Number elevated (>15)<br><15 | <br>17 (68%)<br>8 (32%) |
| AFP (median) | 81.0 |
| hCG (U/L)<br>Number elevated (>5)<br><5 | <br>13 (52%)<br>12 (48%) |
| hCG (median) | 1.0 |
| LDH (U/L)<br>Number elevated (>200)<br>LDH <200 | <br>12 (48%)<br>13 (52%) |
| LDH (median) | 199 |

AFP: Alfa-fetoprotein, hCG: Human chorionic gonadotropin, LDH: Lactate dehydrogenase

When serum tumor markers were examined, AFP levels were elevated in 17 patients (68%), with a median AFP value of 81.0 ng/mL, and hCG levels were elevated in 13 patients (52%), with a median hCG value of 5.0 U/L. LDH levels were above 200 U/L in 12 patients (48%), with a median LDH of 199 U/l. Although the median LDH value was 199 U/L, the cut-off value of >200 U/L was used in accordance with established reference ranges and guideline-based definitions for elevated LDH levels.

According to the IGCCCG classification, 32% of patients were in the intermediate-risk group and 68% were in the good-prognosis group.

In terms of adjuvant chemotherapy, six patients (24%) received two cycles of BEP, five patients (20%) received three cycles, and fourteen patients (56%) received four cycles.

### Univariable Cox Regression Analysis

In univariate Cox analysis, clinical and pathological factors potentially associated with DFS were evaluated. No significant associations were observed between age and T stage (T2 vs. T1) and between age and DFS (p=0.560 and p=0.379, respectively). Tumor location (right vs. left testis) did not affect DFS (p=0.729).

Although patients with rete testis invasion showed a higher tendency to recur, this association was close to but did not reach statistical significance (HR: 8.389; p=0.066). Lymphovascular invasion (LVI) was not significantly associated with DFS (p=0.632).

Predominance of embryonal carcinoma was not a significant predictor of DFS (p=0.863). However, the likelihood of recurrence was significantly lower in patients who received 3 or 4 courses of BEP than in those who received fewer courses (HR: 0.075, p=0.026).

The results of the univariable Cox regression analysis are presented in Table 2.

### Kaplan–Meier Survival Analysis

The median follow-up period of the study was 155.5 months (approximately 13 years). Despite this long follow-up period the median DFS and OS values could not be reached at 10 years because of the low number of observed events (relapses).

**Table 2. Univariable Cox regression analysis of disease free survival**

| Variables | DFS (HR, 95% CI, p value) |
|---|---|
| Age | HR: 1.056 (0.879–1.268), p=0.560 |
| T stage (T1 vs. T2) | HR: 0.362 (0.038–3.483), p=0.379 |
| Tumor side (right vs. left) | HR: 1.415 (0.199–10.055), p=0.729 |
| Rete testis invasion (present vs. absent) | HR: 8.389 (0.869–80.936), p=0.066 |
| Lymphovascular invasion (present vs. absent) | HR: 1.739 (0.181–16.727), p=0.632 |
| BEP cycles (≥3 vs. <3) | HR: 0.075 (0.008–0.733), p=0.026 |
| Embryonal carcinoma predominance (present vs. absent) | HR: 0.841 (0.118–5.978), p=0.863 |

DFS: Disease-free survival, HR: Hazard ratio, CI: Confidence interval, BEP: Bleomycin, etoposide, and cisplatin

The relapse incidence at ten years was approximately 16% (n=4). Kaplan–Meier curves indicate sustained long-term disease control, with the DFS curve presented in Figure 1 and the OS curve in Figure 2. Corresponding 95% CIs were calculated. During follow-up, five deaths were observed: four patients died following disease relapse, and one died from non-disease-related causes without documented evidence of relapse.

## Discussion

This study examined the clinical features and long-term outcomes of individuals diagnosed with stage IS NSGCTs. These findings again demonstrate that stage IS is a rare but difficult-to-manage subgroup of testicular tumors. Persistent elevation of tumor markers following orchiectomy, even if imaging studies are normal, may indicate underlying microscopic metastatic disease; therefore, early systemic treatment is recommended for these patients.

Most studies examining stage IS patients are based on subgroup analyses of larger stage I cohorts. In the study by Klepp et al. (4), NSGCT IS patients had a significantly higher risk of retroperitoneal metastasis after orchiectomy than patients with normal tumor markers. Our study demonstrates that all patients diagnosed with stage IS received systemic chemotherapy and that a rate of recurrence was observed during long-term follow-up, indicating that this patient group exhibits the high metastatic potential reported in the literature.

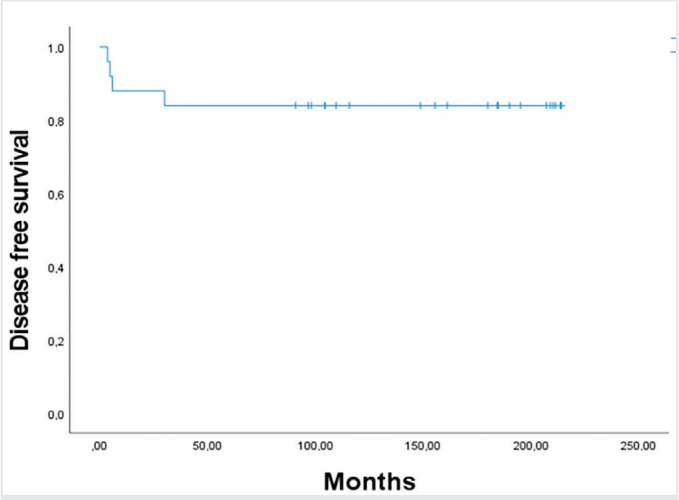


**Figure 1.** Kaplan–Meier curve for disease-free survival

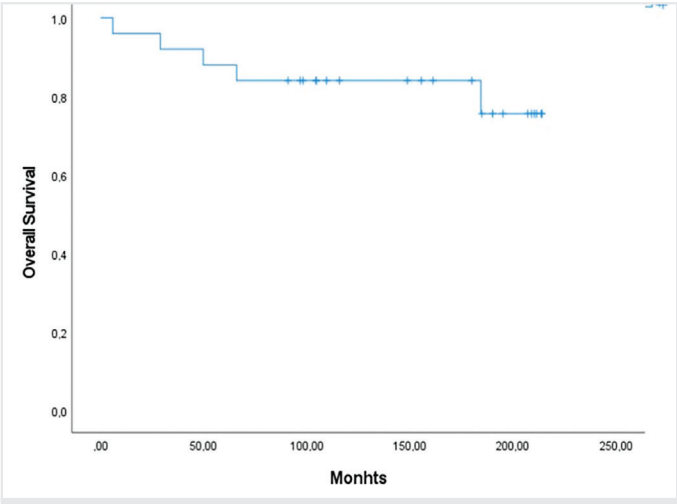


**Figure 2.** Kaplan–Meier curve for overall survival

Although a higher recurrence rate was observed in patients with rete testis invasion in our study, this did not reach statistical significance (HR: 8.389; p=0.066). The prognostic value of rete testis invasion is particularly evident in seminomas (7) , although studies claiming the opposite also exist (8-10). In some studies, an increased risk of metastasis has also been found in NSGCT subgroups (11,12). However, in patients with stage IS, this relationship has not been clearly established previously. Although our findings did not reach statistical significance due to the limited sample size, they suggest that this anatomical invasion may be associated with biologically more aggressive tumor behaviour. Studies with larger samples may more clearly demonstrate the prognostic value of rete testis invasion in stage IS patients.

Our study did not demonstrate a significant effect of LVI on DFS (p=0.632). Numerous studies have shown that LVI is one of the strongest pathological predictors of relapse, particularly in patients with stage I NSGCT (5,13,14). However, it has also been reported that in the large population-based analyses by Albers et al. (15) and by Daugaard et al. (16), the prognostic value of LVI was inconsistent and not significant in some series. Therefore, the lack of significance of LVI for DFS in our study is consistent with the limited sample size and with heterogeneous results reported in the literature. Similarly, no significant association was observed between embryonic carcinoma predominance and DFS (p=0.863). Although embryonal carcinoma may exhibit more aggressive biological behaviour due to its high proliferative capacity, and some studies have shown that a high proportion (>50%) of embryonal carcinoma in the primary tumor is associated with an increased risk of recurrence (13,14), other studies do not support this finding (15,16). The current literature indicates that embryonal carcinoma density does not have clear prognostic value, even in stage I NSGCT. In this context, it is not surprising that our study failed to identify a significant correlation in stage IS patients. These findings may be attributable to reduced statistical power, particularly resulting from the limited sample size. Similarly, a subgroup analysis of DFS according to IGCCCG risk groups was not performed due to the limited sample size and a low event rate.

When tumor location was evaluated in our study, no significant difference in DFS was observed between right- and left-sided testicular tumors (HR: 1.415; 95% CI: 0.199–10.055; p=0.729). This finding is consistent with previous studies in the literature reporting a limited prognostic impact of tumor laterality (17).

A significant reduction in the risk of relapse among patients receiving three to four courses of BEP (HR: 0.075; p=0.026) suggests that treatment intensity may be a critical determinant in patients with stage IS disease (18). The number of cycles administered to patients was determined based on individualized clinical assessments, taking into account treatment-related toxicities, patient tolerance, and physician discretion. Our study supports the notion that administering systemic therapy at a sufficient intensity to the stage IS subgroup is important for long-term disease control. However, larger studies targeting this patient group are

needed to avoid overtreatment and determine the optimal number of courses.

Over the ten-year follow-up period, the incidence of relapse was approximately 16% (n=4). The DFS rate during the same period was found to be 86%. In a study by Aparicio et al. (19) involving 106 stage IS NSGCT patients, the five- and ten-year DFS rates were reported as 87% and 85%, respectively, which demonstrate that our findings are consistent with the literature. These findings indicate that although the vast majority of patients achieve long-term DFS, there remains a certain risk of late recurrence.

In conclusion, stage IS NSGCT represents a heterogeneous group of patients, in whom tumor marker behaviour is decisive for treatment planning. Although cisplatin-based chemotherapy is effective in the vast majority of these patients, certain clinical and pathological factors may influence treatment response. Larger, multicentre, and prospective studies will contribute to a clearer risk classification in this rare patient group and to the optimisation of treatment strategies.

### Study Limitations

The principal limitations of this study include its retrospective nature and the relatively limited patient cohort. However, its long follow-up period and focus on a rare patient group, such as stage IS, are among its strengths. Given the scarcity of data specific to this group in the literature, the findings are expected to contribute to the existing body of knowledge.

## Conclusion

In conclusion, our study confirms that stage IS NSGCT represents a distinct clinical entity characterized by a high probability of subclinical metastasis, necessitating prompt systemic management. We observed favorable long-term oncological outcomes, with a 10-year DFS rate of 86% following cisplatin-based chemotherapy. Notably, the intensity of the treatment regimen appeared to be a critical prognostic factor; patients receiving three or four cycles of BEP chemotherapy demonstrated a significantly lower risk of recurrence than those receiving fewer cycles. While rete testis invasion showed a trend toward an increased risk of recurrence, larger multi-institutional cohorts are required to definitively validate its prognostic significance alongside other pathological markers. Ultimately, strict adherence to standard chemotherapy protocols and rigorous long-term surveillance remain the cornerstones of management to ensure durable disease control in this patient population.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (approval number: 2025/010.99/21/9, date: 30.10.2025).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - E.T., G.A., S.Y., N.S.B., U.D.G., D.I., H.O., N.T.; Concept - E.T., G.A., S.Y., D.I., H.O., N.T.; Design - E.T., S.Y., D.I., H.O., N.T.; Data Collection or Processing - E.T., G.A., S.Y., N.S.B., U.D.G.; Analysis or Interpretation - E.T., D.I., H.O.; Literature Search - E.T., G.A., S.Y., N.S.B., U.D.G., H.O., N.T.; Writing - E.T., G.A., S.Y., N.S.B., U.D.G., N.T.

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# The Effect of Preoperative Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio on the Success of Regional Anesthesia Blocks

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## ABSTRACT

**Introduction:** Effective postoperative pain control is essential for recovery. Peripheral nerve blocks, such as the infraclavicular brachial plexus block, are widely used in multimodal analgesia, but their efficacy may be influenced by systemic inflammation. This study evaluated the predictive value of preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for block efficacy and postoperative pain in upper extremity surgery.

**Methods:** A retrospective cohort of 116 American Society of Anesthesiologists I–II patients (aged 18–93 years) undergoing surgery under an infraclavicular block was analyzed. Preoperative NLR and PLR were calculated from routine blood counts, and patients were stratified into "high" and "low" inflammation groups. Postoperative pain was assessed using the numeric rating scale (NRS) at 1, 6, 12, and 24 hours; tramadol use was recorded. Block success was evaluated by assessing sensory and motor functions.

**Results:** High NLR and PLR were associated with significantly higher NRS scores at 12 and 24 hours ($p<0.001$), greater tramadol use ($p<0.001$), shorter motor block duration, and earlier return of movement.

**Conclusion:** Elevated preoperative NLR and PLR predict reduced infraclavicular block efficacy and greater postoperative pain. These simple, cost-effective biomarkers may aid preoperative risk stratification and guide personalized analgesic strategies.

**Keywords:** Neutrophils, nerve block, postoperative pain, inflammation, inflammation mediators

## Introduction

Effective management of postoperative pain is essential not only for ensuring patient comfort but also for reducing morbidity, facilitating early mobilization, and enhancing overall recovery. Inadequately controlled pain can impair pulmonary function, delay ambulation, prolong hospitalization, and reduce patient satisfaction. Consequently, multimodal analgesia approaches have become standard practice, with regional anesthesia techniques, particularly peripheral nerve blocks, playing a pivotal role in perioperative pain management. These methods have consistently been shown to lower postoperative pain scores, decrease opioid consumption, shorten the length of hospital stay, and support early functional recovery in various surgical populations (1). The success of peripheral nerve blocks is therefore critical; block failure may result in severe pain, the need for additional opioids, and an increased risk of adverse outcomes.

Surgical trauma triggers acute-phase and inflammatory responses, reflected in dynamic changes in circulating immune cells. Specifically, neutrophil counts typically rise, while lymphocyte counts fall, resulting in an elevated neutrophil-to-lymphocyte ratio (NLR). Platelet counts may also increase, contributing to an elevated platelet-to-lymphocyte ratio (PLR). Both NLR and PLR are easily derived from routine complete blood count (CBC) tests and serve as cost-effective, widely available biomarkers of systemic inflammation (2). These markers have been extensively investigated in various medical fields as prognostic indicators and have more recently attracted attention in anesthesiology and perioperative medicine.

Recent surgical studies have shown that elevated preoperative NLR is linked to higher postoperative pain intensity in major orthopedic surgery, while regional anesthesia techniques are associated with lower postoperative NLR and PLR levels, improved analgesia, and reduced opioid requirements. Postoperative NLR values have also shown significant correlations with pain scores in obstetric populations (3-6). In addition, regional anesthesia techniques such as the erector spinae plane block, the adductor canal block, and the IPACK block have been reported to attenuate the inflammatory response, resulting in lower postoperative NLR and PLR values, reduced pain, and improved recovery (7-9).

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These findings highlight the dual role of regional anesthesia in both modulating the surgical stress response and improving analgesia. However, it has been suggested that severe inflammation may compromise the pharmacological efficacy of local anesthetics. For example, reduced tissue pH in inflamed environments increases the proportion of ionized anesthetic molecules, impairing their diffusion across nerve membranes and thereby limiting block effectiveness (10).

Although numerous studies have examined the relationship between postoperative NLR/PLR and pain outcomes, there remains a critical lack of evidence regarding whether preoperative values of these markers can predict the success of peripheral nerve blocks and the severity of postoperative pain. This unresolved issue represents a significant gap in the literature, as identifying high-risk patients before surgery could allow anesthesiologists to anticipate block performance, individualize multimodal analgesic regimens, and optimize perioperative pain strategies.

To address this gap in the literature, this study aimed to evaluate the association of preoperative NLR and PLR with the efficacy of infraclavicular brachial plexus blocks and postoperative pain severity in patients undergoing upper extremity surgery. By focusing on preoperative inflammatory status rather than postoperative changes, this study explores the potential clinical value of baseline immune-inflammatory profiles for anticipating block performance, optimizing perioperative analgesic strategies, and improving individualized patient care.

## Methods

### Study Design and Patient Population

This retrospective observational cohort study was conducted with the approval of the Institutional Ethics Committee of Marmara University Faculty of Medicine (protocol code: 09.2025.25-0179, date: 09.04.2025). The primary objective was to evaluate the association of preoperative NLR and PLR with the efficacy of infraclavicular brachial plexus blocks and the severity of postoperative pain in patients undergoing upper extremity surgery.

In addition to the primary objective, the predefined secondary objectives were to evaluate postoperative pain intensity, measured by numeric rating scale (NRS) scores at 1, 6, 12, and 24 hours; total 24-hour tramadol consumption; and motor block characteristics during the first postoperative day.

Patients were identified through the institutional database, and all eligible cases during the study period were consecutively included according to predefined inclusion and exclusion criteria.

Eligible patients were adults aged 18 years or older who underwent upper limb surgery under infraclavicular brachial plexus block, had an American Society of Anesthesiologists (ASA) physical status of I or II, and had complete clinical and laboratory data available. Patients were excluded if they were younger than 18 years, had an ASA physical status of III or higher, underwent surgery with general anesthesia, had incomplete clinical or laboratory data, or received any postoperative analgesic other than tramadol.

### Preoperative and Intraoperative Data Collection

The following preoperative variables were recorded: age, sex, body mass index (BMI, kg/m²), ASA classification, CBC, NLR, and PLR. Intraoperative data included the duration of surgery and total anesthesia time.

### Postoperative Pain Management and Assessment

Postoperative pain was assessed using the NRS, a validated, unidimensional tool ranging from 0 (“no pain”) to 10 (“worst imaginable pain”). NRS scores were recorded at 1, 6, 12, and 24 hours postoperatively using pain evaluation charts routinely completed by healthcare staff.

Intravenous tramadol was used as the sole rescue analgesic. A dose of 0.5 mg/kg tramadol was administered when the NRS score was ≥4, and total tramadol consumption over the first 24 hours was recorded. To ensure standardization and avoid confounding effects of multiple analgesic regimens, intravenous tramadol was the only rescue option permitted. Patients who required any additional analgesics beyond tramadol were excluded from the analysis.

### Block Technique

All infraclavicular brachial plexus blocks were performed under real-time ultrasound guidance, following the same standardized institutional protocol. A high-frequency linear-array ultrasound transducer was used to identify the brachial plexus cords surrounding the axillary artery. After skin infiltration, the block needle was advanced in-plane under ultrasound guidance. A total of 20 mL of 0.5% bupivacaine was administered. The same local anesthetic agent, concentration, and volume were used in all cases, and all blocks were performed with ultrasound guidance.

### Evaluation of Sensory and Motor Block

Successful block was defined as the presence of effective sensory and motor blockade in the relevant muscle groups innervated by the brachial plexus. Sensory block was evaluated by loss of pinprick sensation in the corresponding dermatomes, while motor block was assessed by inability to move the involved muscle groups. These assessments were recorded at postoperative hours 1, 6, 12, and 24.

All participants exhibited a sustained sensory block at 1 and 6 hours postoperatively. By 12 and 24 hours, the sensory block had fully resolved in all cases. Given the uniform distribution of these findings, no statistical analysis was performed on the sensory block duration.

### Hemodynamic Monitoring

Postoperative hemodynamic parameters , including heart rate, peripheral oxygen saturation ($SpO_2$), and systolic and diastolic blood pressure, were recorded at 1, 6, 12, and 24 hours.

All perioperative data were collected using standardized pain evaluation charts routinely completed by anesthesiology residents under the supervision of the institutional pain management team. To ensure consistency, all staff received prior institutional training in the NRS assessment. Patients with missing clinical or laboratory data were excluded. Preoperative NLR was calculated as the absolute neutrophil

count divided by the lymphocyte count, and PLR as the platelet count divided by the lymphocyte count.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test, and the homogeneity of variances was checked before applying parametric tests. Normally distributed variables were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median (minimum–maximum). Categorical variables were summarized as frequencies and percentages. Patients with missing laboratory or clinical data were excluded according to the predefined exclusion criteria.

Comparisons of continuous variables between two groups were performed using the independent-samples t-test or the Mann–Whitney U test, depending on the data distribution. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate.

Participants were stratified into "low" and "high" NLR and PLR groups based on median values to ensure balanced group sizes and robust intergroup comparisons. In contrast, receiver operating characteristic (ROC) curve–derived cut-off values were used for predictive and clinical interpretation, with the aim of identifying patients at particularly high-risk of inadequate postoperative analgesia, rather than for group stratification. Postoperative pain scores (NRS) and hemodynamic parameters were compared between these groups. To minimize potential confounding, the comparability of the groups was assessed with respect to demographic and intraoperative parameters (age, BMI, ASA classification, surgery duration, and anesthesia time), and no significant differences were observed. The relationship between postoperative pain and NLR was further evaluated using ROC curve analysis. The area under the curve (AUC) was calculated to assess the predictive value. A p value of $<0.05$ was considered statistically significant.

## Results

A total of 132 patients who underwent upper extremity surgery under an infraclavicular brachial plexus block between January 2023 and December 2025 were screened for eligibility. Of these, 16 patients were excluded based on predefined exclusion criteria, and 116 patients were included in the final analysis.

The age range of the study population was 18 to 93 years, with a mean age of 42.58±18.23 years. Of the participants, 105 (90.5%) were male and 11 (9.5%) female.

Participants were stratified into two groups using the median values of NLR (<3.09 vs. ≥3.09) and PLR (<118.4 vs. ≥118.4). No statistically significant differences were observed between the groups for demographic and intraoperative variables ($p>0.05$; Table 1).

There were no statistically significant differences between the low- and high-inflammation groups in terms of surgery duration or anesthesia time (Table 1; $p>0.05$), suggesting that surgical complexity was similar across groups.

Postoperative hemodynamic parameters were comparable between the low- and high-inflammation groups. Although a few isolated time points showed statistically significant differences, these were observed for postoperative 24-hour systolic blood pressure in the NLR groups and for heart rate at postoperative 6, 12, and 24 hours in the PLR groups (Table 2).

Pain assessment using the NRS showed that participants with elevated preoperative inflammatory markers (both NLR ≥3.09 and PLR ≥118.4) had significantly higher pain scores at postoperative hours 1, 12, and 24. These patients also required significantly greater tramadol consumption within the first 24 hours (all $p<0.001$; Table 3).

Persistence of motor block at postoperative hours 6, 12, and 24 was more frequent in both the high NLR and high PLR groups (all $p<0.05$). This indicates that elevated systemic inflammation is consistently associated with delayed motor recovery (Table 4).

ROC curve analysis demonstrated that NLR predicted postoperative pain with an AUC of 0.711 (95% confidence interval: 0.617–0.825; $p<0.001$). An NLR cut-off of >3.78 yielded 46.2% sensitivity and 100.0% specificity (Figure 1).

## Discussion

In this study, we evaluated whether preoperatively determined NLR and PLR were associated with the success of infraclavicular brachial plexus blocks and postoperative pain intensity. The findings indicate that an elevated preoperative systemic inflammatory state, reflected by high NLR and PLR values, is associated with reduced block effectiveness and worse postoperative pain outcomes in upper extremity surgery. These results support our initial hypothesis that systemic inflammation may negatively influence both the success of the block and the severity of postoperative pain.

Participants with higher preoperative NLR and PLR values exhibited greater persistence of motor block, a delay in motor recovery, and significantly higher pain scores at 12 and 24 hours postoperatively. These findings indicate that a pro-inflammatory physiological environment may alter the pharmacodynamic profile of local anesthetics, resulting in prolonged motor blockade but reduced analgesic effectiveness. This dissociation between motor and sensory block suggests that inflammation may differentially affect nerve fiber types and pain pathways, leading to poorer pain control despite longer motor block duration.

Although NLR demonstrated a moderate discriminative ability for predicting postoperative pain (AUC: 0.711), the combination of its very high specificity (100%) and relatively low sensitivity (46.2%) indicates that it may be more useful for identifying patients at particularly high-risk of inadequate analgesia rather than as a broad screening tool. In this context, elevated preoperative NLR values may help anesthesiologists recognize individuals who would benefit most from intensified or personalized analgesic strategies, even though a normal NLR does not exclude the possibility of suboptimal pain control.

**Table 1. Comparison of demographic and intraoperative parameters according to median NLR and PLR values**

| Parameter | Low NLR (<3.09) | High NLR (≥3.09) | p value |
|---|---|---|---|
| Age (years) | 43.05±18.77 | 42.09±17.85 | 0.777 |
| BMI (kg/m$^2$) | 26.5±4.6 | 25.7±3.9 | 0.325 |
| ASA score median (25-75) | 1(1-2) | 1(1-2) | 0.304 |
| Duration of surgery (minute) | 147.76±62.47 | 159.31±49.41 | 0.272 |
| Duration of anesthesia (minute) | 155.60±61.33 | 167.24±49.36 | 0.263 |
| **Parameter** | **Low PLR (<118.4)** | **High PLR (≥118.4)** | **p value** |
| Age (years) | 41.27±18.91 | 43.91±17.59 | 0.438 |
| BMI (kg/m$^2$) | 26.1±4.5 | 25.9±4.2 | 0.798 |
| ASA score median (25-75) | 1 (1-2) | 1(1-2) | 0.530 |
| Duration of surgery (minute) | 151.86±61.83 | 155.26±50.61 | 0.747 |
| Duration of anesthesia (minute) | 160.17±60.86 | 162.72±50.38 | 0.807 |

Data are presented as mean ± standard deviation for normally distributed variables and as median ($25^{th}$–$75^{th}$ percentiles) for non-normally distributed variables. Either the independent-samples t-test or the Mann–Whitney U test was used for continuous variables; the chi-square test was used for categorical variables
$p<0.05$ was considered statistically significant
NLR: Neutrophil-to-lymphocyte ratio, BMI: Body mass index, ASA: American Society of Anesthesiologists, PLR: Platelet-to-lymphocyte ratio

**Table 2. Comparison of postoperative vital signs by median NLR and PLR groups**

| Parameter | Low NLR (<3.09) | High NLR (≥3.09) | p value |
|---|---|---|---|
| Postop 1$^{st}$ hr HR (bpm) | 74.05±11.97 | 75.34±11.26 | 0.550 |
| Postop 6$^{th}$ hr HR (bpm) | 76.14±9.31 | 75.00±8.88 | 0.502 |
| Postop 12$^{th}$ hr HR (bpm) | 76.29±9.16 | 76.09±9.28 | 0.904 |
| Postop 24$^{th}$ hr HR (bpm) | 75.97±8.18 | 78.55±10.27 | 0.136 |
| Postop 1$^{st}$ hr SBP (mmHg) | 126.47±16.06 | 128.22±20.04 | 0.603 |
| Postop 6$^{th}$ hr SBP (mmHg) | 123.38±11.59 | 125.97±10.39 | 0.208 |
| Postop 12$^{th}$ hr SBP (mmHg) | 119.76±9.62 | 122.72±12.72 | 0.159 |
| Postop 24$^{th}$ hr SBP (mmHg) | 120.14±10.54 | 124.33±11.60 | 0.044 |
| Postop 1$^{st}$ hr DBP (mmHg) | 76.93±10.73 | 79.21±12.21 | 0.288 |
| Postop 6$^{th}$ hr DBP (mmHg) | 72.55±8.91 | 73.64±7.49 | 0.479 |
| Postop 12$^{th}$ hr DBP (mmHg) | 74.84±10.85 | 75.67±10.89 | 0.683 |
| Postop 24$^{th}$ hr DBP (mmHg) | 74.36±10.88 | 74.72±9.90 | 0.852 |
| **Parameter** | **Low PLR (<118.4)** | **High PLR (≥118.4)** | **p value** |
| Postop 1$^{st}$ hr HR (bpm) | 73.10±10.80 | 76.35±12.22 | 0.132 |
| Postop 6$^{th}$ hr HR (bpm) | 73.69±9.54 | 77.51±8.20 | 0.023 |
| Postop 12$^{th}$ hr HR (bpm) | 74.51±8.74 | 77.93±9.37 | 0.044 |
| Postop 24$^{th}$ hr HR (bpm) | 74.20±7.56 | 80.42±9.98 | 0.001 |
| Postop 1$^{st}$ hr SBP (mmHg) | 128.41±14.43 | 126.25±21.33 | 0.523 |
| Postop 6$^{th}$ hr SBP (mmHg) | 124.90±10.27 | 124.44±11.87 | 0.824 |
| Postop 12$^{th}$ hr SBP (mmHg) | 119.69±10.08 | 122.84±12.36 | 0.135 |
| Postop 24$^{th}$ hr SBP (mmHg) | 121.32±10.27 | 123.18±12.17 | 0.377 |
| Postop 1$^{st}$ hr DBP (mmHg) | 77.12±11.58 | 79.05±11.44 | 0.367 |
| Postop 6$^{th}$ hr DBP (mmHg) | 72.12±8.40 | 74.11±7.96 | 0.194 |
| Postop 12$^{th}$ hr DBP (mmHg) | 75.00±11.77 | 75.53±9.87 | 0.795 |
| Postop 24$^{th}$ hr DBP (mmHg) | 74.64±11.35 | 74.44±9.31 | 0.915 |

Vital signs were treated as continuous variables and presented as mean ± standard deviation because they were normally distributed. Between-group comparisons were made using the independent-samples t-test
$p<0.05$ was considered statistically significant
hr: hour, HR: Heart rate, postop: Postoperative, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

**Table 3. Distribution of postoperative NRS scores and total opioid dose according to median NLR and PLR**

| Parameter | Low NLR (<3.09) | High NLR (≥3.09) | p value |
|---|---|---|---|
| Postop 1st hr NRS | 0 (0-0) | 0 (0-1) | 0.030 |
| Postop 6th hr NRS | 0 (0-1) | 1 (0-1) | 0.153 |
| Postop 12th hr NRS | 0 (0-0) | 1 (1-3) | 0.001 |
| Postop 24th hr NRS | 0(0-1) | 1 (1-3) | 0.001 |
| Postop total tramadol dose (mg) | 0 (0-75) | 100 (0-200) | <0.001 |
| **Parameter** | **Low PLR (<118.4)** | **High PLR (≥118.4)** | **p value** |
| Postop 1st hr NRS | 0(0-0) | 0 (0-1) | 0.013 |
| Postop 6th hr NRS | 0 (0-0) | 0 (0-1) | 0.448 |
| Postop 12th hr NRS | 1(0-1) | 2 (1-3) | <0.001 |
| Postop 24th hr NRS | 0 (0-1) | 3 (3-3) | <0.001 |
| Postop total tramadol dose (mg) | 0 (0-100) | 100 (0-200) | <0.001 |

Pain scores and opioid doses are presented as median (25th–75th percentiles). Comparisons between groups were made using the Mann–Whitney U test
p<0.05 was considered statistically significant
hr: hour, postop: Postoperative, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, NRS: Numeric rating scale

**Table 4. Persistence of motor block at postoperative hours 1, 6, 12, and 24 according to NLR and PLR groups**

| Time | Low NLR (<3.09) | High NLR (≥3.09) | p value |
|---|---|---|---|
| 1st hr | 0 (0) | 1 (1.7%) | 0.315 |
| 6th hr | 0 (0) | 6 (10.3) | 0.012 |
| 12th hr | 0 (0) | 37 (63.8%) | <0.001 |
| 24th hr | 2 (3.4%) | 40 (69.0%) | <0.001 |
| **Time** | **Low PLR (<118.4)** | **High PLR (≥118.4)** | **p value** |
| 1st hr | 0 (0%) | 1 (98.2%) | 0.307 |
| 6th hr | 0 (0%) | 6 (10.5%) | 0.010 |
| 12th hr | 5 (8.5%) | 32 (56.1%) | <0.001 |
| 24th hr | 7 (11.9%) | 35 (61.4%) | <0.001 |

Categorical data are presented as numbers (percentages). Chi-square or Fisher's exact tests were for comparisons, depending on expected frequencies
p<0.05 was considered statistically significant
hr: hour, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

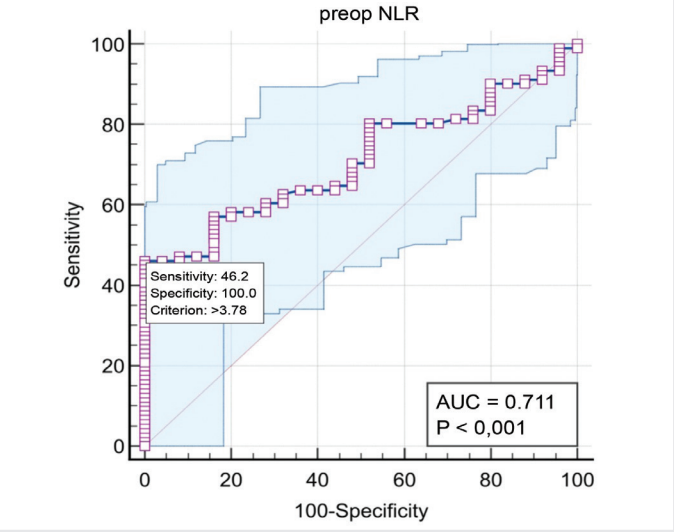


**Figure 1.** ROC curve showing the predictive power of NLR for postoperative pain presence
Preop: Preoperative, NLR: Neutrophil-to-lymphocyte ratio, ROC: Receiver operating characteristic, AUC: Area under the curve

Our findings agree with existing literature highlighting the complex relationship between inflammation, anesthetic techniques, and postoperative pain and thereby contribute to the growing evidence in this field (3,11,12). Elevated preoperative NLR has previously been associated with increased postoperative pain in cervical disc herniation (13), and with higher analgesic requirements in orthognathic surgery (14). However, most prior studies focused on NLR without evaluating PLR or applying standardized regional anesthesia techniques. Consistent with our results, Surhonne et al. (15) demonstrated that postoperative increases in leukocyte count and NLR were significantly attenuated in patients receiving spinal anesthesia compared with those under general anesthesia. Our findings extend these results by demonstrating that not only postoperative changes but also preoperative inflammatory status can significantly influence regional block success and pain outcomes. This supports the hypothesis that regional anesthesia suppresses the inflammatory response to surgical trauma. Furthermore, most available studies have either measured inflammatory markers postoperatively or included patients managed under general anesthesia (16,17).

Our study focused on the relationship between preoperative inflammatory status and the success of infraclavicular brachial plexus block, whereas Yeniay et al. (18) recently demonstrated, in a cesarean cohort, that elevated NLR, PLR, and other inflammatory indices were significantly associated with shorter durations of sensory and motor block under spinal anesthesia. Taken together, these findings indicate that systemic inflammation can adversely affect the success of regional anesthesia blocks; however, the magnitude of this effect and clinical implications may vary according to block type and patient population. By examining preoperative inflammatory status within the context of a standardized regional block, our study provides novel insight into how baseline inflammation can influence the success of the regional block and subsequent pain outcomes.

Several biologically grounded mechanisms may explain why preoperative systemic inflammation reduces the efficacy of local anesthetics. Inflammation is often accompanied by tissue acidosis, which lowers pH and shifts local anesthetics into their ionized form, thereby limiting their ability to penetrate nerve membranes and block sodium channels (19). Elevated NLR or PLR, as markers of increased systemic inflammation, may therefore compromise anesthetic diffusion into nerve fibers and shorten block duration. In addition, inflammation-induced vasodilation increases regional blood flow, thereby accelerating drug clearance from the injection site (20). Beyond these pharmacokinetic effects, neuroinflammatory mediators such as interleukin-1 beta, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) sensitize nociceptors, alter sodium channel expression, and promote glial activation, collectively enhancing neuronal excitability and lowering pain thresholds (21). Consequently, patients with elevated preoperative inflammatory markers are more likely to experience lower block success rates, more rapid resolution of anesthesia, and increased postoperative pain.

It is well established that regional anesthesia can modulate immune and inflammatory responses, and studies have shown that nerve blocks can reduce the surgical stress response and attenuate the release of pro-inflammatory cytokines (11,12). This bidirectional interaction suggests that while regional techniques can mitigate inflammatory responses, their analgesic efficacy can be compromised by the same systemic inflammatory processes. These mechanisms provide a rationale for incorporating preoperative inflammatory markers into clinical decision-making and tailoring analgesic strategies accordingly.

From a clinical perspective, preoperative NLR and PLR are simple, cost-effective markers that could be integrated into preoperative assessment. Patients with elevated values stand to benefit from personalized multimodal analgesia that incorporates preemptive approaches, continuous catheter-based techniques, and adjuvants to prolong and potentiate block success. Accordingly, NLR and PLR should be regarded not only as prognostic markers but also as as practical decision-making tools that can assist anesthesiologists in tailoring perioperative analgesic strategies.

In particular, agents such as dexamethasone or α2-agonists have been shown to help mitigate the negative impact of systemic inflammation on nerve block success and improve postoperative pain outcomes. These approaches align with the broader shift toward individualized pain management (22,23). Moreover, strategies aimed at reducing inflammation before surgery—such as preoperative NSAIDs (24), other anti-inflammatory agents, or optimization of comorbid conditions and nutritional status—are expected to further improve block success and postoperative outcomes. Future studies should investigate whether preoperative inflammatory profiles affect not only acute postoperative pain but also long-term outcomes, including the risk of chronic postsurgical pain.

### Study Limitations

This study has several limitations. Peripheral nerve blocks were not performed by a single practitioner, which may have introduced variability despite standardized protocols. The relatively small sample size, heterogeneity in surgical procedures (e.g., urgent vs. elective, fracture fixation vs. tendon repair), and the lack of assessment of procedure-specific effects or inflammatory markers (IL-6, TNF-α) may have limited the mechanistic interpretation of our findings. Postoperative analgesia was restricted to intravenous tramadol, thereby ensuring standardization but not reflecting real-world multimodal practice. Additionally, because this was a retrospective study using electronic records, selection and measurement biases cannot be excluded. In addition, the inconsistent reporting of PLR compared to NLR in the current literature represents an unresolved limitation, likely reflecting variability in patient populations, cut-off values, and methodological differences. Larger prospective, randomized studies in homogeneous populations using standardized block techniques are warranted. Finally, the use of median-based grouping for statistical comparisons, together with ROC-derived cut-off values for predictive interpretation, may appear methodologically inconsistent; however, this approach reflects the dual aims of the study, combining statistical robustness with clinically meaningful risk stratification.

## Conclusion

Our findings suggest that easily accessible preoperative inflammatory biomarkers, such as the NLR and PLR, are associated with both the efficacy of peripheral nerve blocks and postoperative pain scores. Elevated systemic inflammation, indicated by high NLR or PLR values, is associated with reduced block effectiveness and increased postoperative pain. Among these markers, NLR emerged as the stronger and more reliable predictor, whereas PLR provided supplementary but less consistent information. Incorporating these biomarkers into preoperative assessments could help anesthesiologists identify patients at greater risk of inadequate postoperative analgesia and guide the use of personalized strategies, such as multimodal regimens, adjuvants, or continuous catheter techniques. However, given the relatively small sample size and variability in block administration in our study, these results should be interpreted with caution and validated in larger, prospective trials. In summary, preoperative evaluation of NLR and PLR holds promise as a simple and cost-effective approach to support individualized perioperative pain management.

### Ethics

**Ethics Committee Approval:** This study was conducted with the approval of the Institutional Ethics Committee of Marmara University Faculty of Medicine (protocol code: 09.2025.25-0179, date: 09.04.2025).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Concept - G.Ç., D.G.; Design - G.Ç.; Data Collection or Processing: D.G.; Analysis or Interpretation: D.G.; Literature Search: G.Ç., D.G.; Writing: G.Ç.

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

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