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**Phone:** +90 (530) 177 30 97 / +90 (539) 307 32 03
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# Diabetes Subtypes and Urinary Incontinence in Pregnancy: Role of BMI and HbA1c

Zeynep Kayaoğlu Yıldırım, Cansu Tekin, Hale Özer Çaltek

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye

## ABSTRACT

**Introduction:** Urinary incontinence (UI) is a significant health concern affecting the quality of life of many pregnant women worldwide. This study examined the relationship between diabetes mellitus (DM) and UI during pregnancy and postpartum, focusing on metabolic factors like body mass index (BMI) and glycemic control.

**Methods:** A prospective observational study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, including 147 pregnant women in their third trimester (≥30 weeks). Participants were categorized into type 1 DM (T1DM) (n=16), type 2 DM (n=32), gestational DM (GDM) (n=51), and a control group (n=48). UI was assessed using the International Consultation on Incontinence Questionnaire-Short Form, and metabolic parameters were retrieved from hospital records. Subgroup comparisons and receiver operating characteristic (ROC) curve analysis determined BMI and hemoglobin A1c (HbA1c) cut-off values for predicting postpartum UI.

**Results:** Higher HbA1c levels were significantly associated with increased incontinence severity in GDM ($p<0.0001$), but not in other diabetes subgroups. BMI effects varied: in T1DM, a higher BMI correlated with less severe incontinence, whereas in GDM, it was linked to more severe incontinence. Postpartum UI was associated with elevated BMI in T1DMand GDM groups. ROC analysis identified optimal thresholds for predicting postpartum UI: HbA1c =5.75% [area under the curve (AUC) =0.672, sensitivity =61%, specificity =77%] and BMI =32.75 (AUC =0.627, sensitivity =65%, specificity =61%).

**Conclusion:** BMI and glycemic control significantly impact UI severity and postpartum persistence, particularly in GDM and T1DM. Identifying BMI and HbA1c as predictive markers underscores the need for targeted metabolic interventions.

**Keywords:** Urinary incontinence, pregnancy, postpartum, diabetes mellitus, BMI, glycemic control

## Introduction

Urinary incontinence (UI) is a significant health concern affecting the quality of life of many pregnant women worldwide. The International Incontinence Society defines UI as the involuntary leakage of urine (1). UI during pregnancy is a prevalent condition, with reported rates ranging from 14.7% to 84.5% across different regions (2-9). Despite its high prevalence, the underlying risk factors and mechanisms remain incompletely understood.

Diabetes mellitus (DM) has been identified as a potential contributor to UI (4-13). In patients with diabetes, the risk of UI is reported to be 2.5 times higher due to declines in muscle strength and physical function. Additionally, gestational DM (GDM) is associated with an increased risk of UI (14). Studies have suggested that type 2 DM (T2DM) may contribute to UI. Research has identified diabetes as an independent risk factor for UI, with additional influences of age, obesity, and child-bearing history (15). In contrast, UI in women with type 1 DM (T1DM) is frequently observed alongside other diabetes-related complications such as neuropathy, retinopathy, and nephropathy (16). Glycosuria, microvascular damage, and neuropathy have been proposed as key contributing factors. Furthermore, inadequate glycemic control has been linked to an elevated risk of developing UI in women with diabetes (16).

Although previous studies have explored the association between DM and UI, the specific impact of different types of diabetes on maternal UI during pregnancy and postpartum remains unclear. Therefore, this study aimed to identify independent risk factors for pregnancy-related and postpartum UI with a particular focus on the role of different types of DM.

## Methods

This prospective observational study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital

**Address for Correspondence:** Zeynep Kayaoğlu Yıldırım MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye
**E-mail:** drkayaoglu@hotmail.com **ORCID ID:** orcid.org/0000-0002-2582-7675

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between November 2024 and February 2025 with participants recruited from the perinatology department. A total of 147 pregnant women in their third trimester (≥30 weeks) were enrolled and categorized into four groups: T1DM group (n=16), T2DM group (n=32), GDM group (n=51), and a control group (CG) consisting of healthy pregnant women with uncomplicated pregnancies (n=48). Participants were aged between 18 and 40 years and had good physical and mental health. Eligibility criteria included singleton pregnancy, gestational age of at least 30 weeks, and no history of known urological disorders; while exclusion criteria encompassed multiple pregnancies, chronic kidney disease, and prior urogynecological surgery.

The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinical Research Ethics Committee (approval number: 2022-296, date: 19.11.2024). Written informed consent was obtained from all participants.

Maternal age, insulin use, and history of pre-pregnancy UI were obtained through direct patient interviews. Third-trimester hemoglobin A1c (HbA1c) levels and complete urinalysis results were extracted from the hospital's digital medical records. UI was assessed using the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) 17, a validated instrument with a Cronbach's alpha of 0.88. This tool consists of four items: three scored questions evaluating leakage frequency (0-5), volume (0-6), and impact on quality of life (0-10), summing to a total score of 0-21, and one unscored question identifying situations where incontinence occurs.

To minimize selection bias, only participants meeting strict inclusion and exclusion criteria were enrolled. The study size was determined based on previous studies to ensure adequate statistical power for subgroup analyses.

### Statistical Analysis

Descriptive statistics summarized the demographic and clinical characteristics, with continuous variables expressed as medians (interquartile ranges) and categorical variables as counts (percentages). Subgroup analyses examined the associations between incontinence severity and age, body mass index (BMI), HbA1c, insulin use, and UTI history, using Wilcoxon rank-sum tests for continuous data and chi-square or Fisher's exact tests for categorical data. Predictive analysis involved receiver operating characteristic (ROC) curve analysis to identify optimal cut-off values for HbA1c and BMI in predicting incontinence prepartum and postpartum, with discriminatory ability assessed using area under the curve (AUC) and sensitivity and specificity calculated for identified thresholds. Statistical significance was set at $p<0.05$.

## Results

A total of 147 participants were included in the final analysis. The study groups comprised 16 women with T1DM, 32 with T2DM, 51 with GDM, and 48 healthy pregnant women in the CG.

When evaluating the relationship between incontinence severity during pregnancy and various metabolic and clinical factors across different diabetes subgroups, higher HbA1c levels were significantly associated with increased incontinence severity in women with GDM ($p<0.0001$), while no significant association was observed in other diabetes subgroups. The effect of BMI on incontinence severity differed among groups; in the T1DM group, a higher BMI was associated with lower incontinence severity, whereas in the GDM group, a higher BMI correlated with more severe incontinence. Insulin use, maternal age, and UTI history did not significantly impact on incontinence severity in any diabetes subgroup (Table 1).

Postpartum incontinence persistence was analyzed in relation to BMI, HbA1c levels, insulin use, and UTI history. A higher BMI was identified as a significant risk factor for postpartum incontinence in women with T1DM and GDM, while no such association was found in non-diabetic women or those with T2DM. Elevated HbA1c levels were significantly linked to postpartum incontinence in patients with T1DM but not in other groups. In the T1DM group, women with postpartum incontinence

**Table 1. Relationship between diabetes subtypes and incontinence severity during pregnancy**

| Diabetes type | Control group | | Type 1 diabetes | | Type 2 diabetes | | GDM | |
|---|---|---|---|---|---|---|---|---|
| | Incontinence score | p | Incontinence score | p | Incontinence score | p | Incontinence score | p |
| Age (year) | 0.224 | 0.124 | -0.26 | 0.148 | 0.028 | 0.843 | 0.323 | 0.222 |
| BMI (kg/m$^2$) | 0.002 | 0.987 | -0.388 | 0.028 | 0.036 | 0.802 | 0.499 | 0.049 |
| HbA1c (%) | 0.078 | 0.597 | 0.188 | 0.303 | 0.223 | 0.114 | 0.82 | <0.0001 |
| | Median (IQR) | p | Median (IQR) | p | Median (IQR) | p | Median (IQR) | p |
| Insulin use | | | | | | | | |
| Yes | 1 (1-4.25) | | 6.5 (2-11.8) | | 1 (1-5) | | 10 (0-16.5) | |
| No | | | 6 (1-11.5) | 0.901 | 1 (1-3.25) | 0.716 | 1 (1-1) | 0.609 |
| UTI | | | | | | | | |
| No | 1 (1-1) | | 6 (1-12) | | 1 (1-5) | | 1 (1-7.8) | |
| Yes | 1 (1-6) | 0.116 | 4.5 (1.8-5.8) | 0.488 | 1 (1-1) | 0.246 | 3.5 (2.3-4.8) | 0.733 |

This table analyzes incontinence severity across diabetes subgroups: HbA1c: higher levels worsen incontinence in GDM ($p<0.0001$), but not in other types. BMI: In T1D, higher BMI is associated with milder incontinence; in GDM, it is associated with greater severity of incontinence. Insulin use and UTI history: no significant impact.
BMI: Body mass index, HbA1c: Hemoglobin A1c, UTI: Urinary tract infection, GDM: Gestational diabetes mellitus, T1D; Type 1 diabetes, IQR: Interquartile range

**Table 2. Postpartum incontinence and its association with BMI, HbA1c, insulin use, and UTI across diabetes subtypes**

| Diabetes type | Control group | | | T1D | | | T2D | | | GDM | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Postpartum incontinence | | | Postpartum incontinence | | | Postpartum incontinence | | | Postpartum incontinence | | |
| | No | Yes | | No | Yes | | No | Yes | | No | Yes | |
| | Median (IQR) | Median (IQR) | p | Median (IQR) | Median (IQR) | p | Median (IQR) | Median (IQR) | p | Median (IQR) | Median (IQR) | p |
| Age (year) | 28 (22-36) | 31 (25-38) | 0.38 | 25 (20-39) | 31 (25-33) | 0.17 | 33 (28-42) | 31 (28-39) | 0.484 | 33 (27-38) | 33 (-34 | 0.806 |
| BMI (kg/m²) | 30 (23.1-35.5) | 28.4 (25.5-38.0) | 0.97 | 23.8 (-32.0) | 30 (26-36) | 0.013 | 36.0 (25.4-47.0) | 35.8 (33.0-41.9) | 0.826 | 33.5 (29.0-40.1) | 42 (-43.0) | 0.039 |
| HbA1c (%) | 4.9 (4.6-5.3) | 5.1 (4.8-6.1) | 0.275 | 6.2 (5.8-7.2) | 7.0 (6.4-7.2) | 0.02 | 5.6 (5.1-9.4) | 5.8 (4.6-7.3) | 0.704 | 5.3 (5.1-6.8) | 5.3 (-5.4) | 0.925 |
| Insulin use | | | | | | | | | | | | |
| Yes | | | | 9 (75.0) | 0 | | 14 (73.7) | 11 (91.7) | | 25 (52.1) | 1 (33.3) | |
| No | 44 | 4 | | 3 (25.0) | 4 (100.0) | 0.019 | 5 (26.3) | 1 (8.3) | 0.407 | 23 (47.9) | 2 (66.7) | 0.61 |
| UTI | | | 0.155 | | | 1 | | | 0.407 | | | 1 |
| No | 37 (84.1) | 2 (50.0) | | 10 (83.3) | 4 (100.0) | | 14 (73.7) | 11 (91.7) | | 36 (75.0) | 3 (100.0) | |
| Yes | 7 (15.9) | 2 (50.0) | | 2 (16.7) | 0 | | 5 (26.3) | 1 (8.3) | | 12 (25.0) | 0 | |

This table compares post-pregnancy incontinence across diabetes types: age and UTI history: no significant impact (p>0.05).
BMI: Higher BMI is linked to incontinence in T1D (p=0.013) and GDM (p=0.039) but not in T2D or non-diabetics. HbA1c: higher levels of HbA1c increase incontinence risk in T1D (p=0.02). Insulin use: in T1D, incontinent women were less likely to use insulin (p=0.019).
BMI: Body mass index, HbA1c: Hemoglobin A1c, UTI: Urinary tract infection, GDM: Gestational diabetes mellitus, T1D: Type1 diabetes, T2D: Type 2 diabetes, IQR: Interquartile range

were less likely to use insulin than those without. Age and UTI history were not significantly associated with postpartum incontinence in any diabetes group (Table 2).

ROC curve analysis was conducted to determine optimal cut-off values for prepartum BMI and HbA1c in predicting postpartum incontinence persistence. The analysis identified the following thresholds: prepartum HbA1c level [for AUC =0.672, for 95% confidence interval (CI): 0.545-0.800, for cut-off =5.75%, for sensitivity =61%, for specificity = 77%] and prepartum BMI (for AUC = 0.627, for 95% CI: 0.51–0.75, for cut-off = 32.75, for sensitivity =65%, for specificity =61%) (Table 3). These findings suggest that elevated prepartum HbA1c and BMI may serve as predictors of postpartum UI persistence in certain subgroups.

## Discussion

This study aimed to explore the relationship between different types of DM and UI during pregnancy and the postpartum period. These findings provide valuable insights into the independent risk factors contributing to UI, particularly in women with GDM and T1DM.

A key observation in our study was that higher HbA1c levels were significantly associated with an increased severity of incontinence in women with GDM. This aligns with previous research suggesting that hyperglycemia contributes to UI through microvascular damage, glycosuria-induced polyuria, and impaired neuromuscular function (18). Some studies have reported a positive correlation between HbA1c levels and UI severity (18,19), but in our study, no such association was found in women with T1DM or T2DM. This suggests potential differences in the pathophysiology of UI among different diabetes subtypes. Similarly, Valerio et al. (19) found no association between HbA1c and UI in pregnant women with T1DM. However, our results contrast with those of previous studies linking poor glycemic control to UI in T2DM patients, highlighting the need for further investigation.

BMI is another significant factor influencing UI severity and postpartum incontinence persistence (10,19). In GDM, a higher BMI was correlated with an increase in incontinence severity, whereas in T1DM, a higher BMI was unexpectedly associated with lower incontinence severity. This discrepancy may be due to the differences in body composition and muscle function between these groups, warranting further research to clarify the underlying mechanisms. Importantly, our findings demonstrated that a high BMI was a strong predictor of postpartum incontinence persistence in both the T1DM and GDM groups, emphasizing the need for targeted weight management interventions to reduce the risk of UI in these populations.

Our results also showed that insulin use did not significantly impact UI severity during pregnancy in any of the diabetes subgroups. However, in the postpartum period, women with T1DM who developed persistent incontinence were less likely to have used insulin, suggesting the potential protective effect of insulin therapy. As no prior studies have specifically investigated this association, further research is required to determine whether insulin directly influences pelvic floor neuromuscular function or serves as a marker of better overall glycemic control.

Interestingly, maternal age and history of urinary tract infection were not significantly associated with UI severity or postpartum incontinence in any diabetes group. This contrasts with previous studies that identified age as a risk factor for UI (20). One possible explanation is that, in our relatively young study population (18-40 years), diabetes-related metabolic and hormonal changes may have played a more dominant role than age-related pelvic floor deterioration.

ROC curve analysis provided clinically relevant cut-off values for BMI

**Table 3. ROC curve analysis for BMI and HbA1c cut-off values in predicting postpartum incontinence**

| Paramater | AUC | 95% CI | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| HbA1c (%) | 0.672 | 0.545-0.80 | 5.75 | 0.61 | 0.77 |
| BMI (kg/m$^2$) | 0.627 | 0.51-0.75 | 32.75 | 0.65 | 0.61 |

ROC curve analysis identified optimal cut-off values for BMI and HbA1c predictive of incontinence: prepartum HbA1c: area under the curve (AUC) =0.663 (95% CI: 0.442-0.884). Postpartum HbA1c: AUC =0.672 (95% CI: 0.545-0.800), cut-off =5.75%, sensitivity =61%, specificity =77%. Postpartum BMI: AUC =0.627 (95% CI: 0.51-0.75), cut-off =32.75, sensitivity =65%, specificity =61%.
ROC: Receiver operating characteristic curve, BMI: Body mass index, HbA1c: Hemoglobin A1c, CI: Confidence interval

(32.75) and HbA1c (5.75%) for predicting postpartum incontinence persistence. While these thresholds demonstrated moderate sensitivity and specificity, they also highlighted the potential utility of BMI and glycemic control as predictive markers for postpartum UI.

### Study Limitations

This study has several limitations that should be considered when interpreting the findings. First, the relatively small sample size, particularly in the T1DM group, may have reduced the statistical power to detect certain associations and limited the generalizability of the results. Second, potential contributing factors such as mode of delivery, parity, and physical activity levels were not assessed, which could independently influence the risk of UI. Third, the study relied on self-reported UI symptoms via the ICIQ-SF questionnaire, introducing the possibility of recall bias or subjective misclassification. Future research should focus on larger, multicenter, and longitudinal studies to validate and expand upon these results and to investigate additional mechanisms linking diabetes subtypes, BMI, and glycemic control to UI.

## Conclusion

In conclusion, our study highlights the significant impact of BMI and glycemic control on UI severity during pregnancy and postpartum incontinence persistence, particularly in women with GDM or T1DM. The identification of BMI and HbA1c as predictive markers underscores the need for targeted interventions aimed at optimizing weight and glycemic control to reduce UI risk in high-risk populations. Future research should further elucidate the underlying mechanisms and explore effective management strategies to improve maternal pelvic health.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinical Research Ethics Committee (approval number: 2022-296, date: 19.11.2024).

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

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - Z.K.Y., C.T. H.Ö.Ç.; Concept - Z.K.Y.; Design - Z.K.Y.; Data Collection or Processing - C.T. H.Ö.Ç; Analysis or Interpretation – Z.K.Y.; Literature Search - Z.K.Y., C.T. H.Ö.Ç.; Writing – Z.K.Y.

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# Evaluation of the Effects of Anesthetics and Surgery on Sleep Quality in Patients Undergoing Posterior Spinal Instrumentation Surgery: A Prospective Randomised Clinical Trial

Selcan Akesen[1], Gökay Eken[2], Yücel Bilgin[2], Saltuk Buğra Güler[2], Elifgül Ulutaş[1]

[1]Bursa Uludağ University Faculty of Medicine, Department of Anesthesiology and Reanimation, Bursa, Türkiye
[2]Bursa Uludağ University Faculty of Medicine, Department of Orthopedics and Traumatolology, Bursa, Türkiye

## ABSTRACT

**Introduction:** The aim of the study is to evaluate the impact of the anesthesia methods and surgical procedure on the sleep patterns and sleep quality of patients undergoing posterior spinal instrumentation, using the Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

**Methods:** A total of 40 patients, American Society of Anesthesiology I-III, aged 18 and over who underwent elective spinal posterior instrumentation were included. The patients were divided into two groups randomly-those with sevoflurane-remifentanil anesthesia and those with total intravenous anesthesia-using the closed envelope method. Patients were evaluated before and after surgery for sleep quality using the PIRS-20 one month before surgery and on the 7$^{th}$ day postoperatively, for pain using the Visual Analog Scale (VAS) recorded one night before surgery and the first hour postoperatively, and for anxiety using the State-Trait Anxiety Inventory (STAI) recorded one night before surgery and on the 7$^{th}$ day postoperatively.

**Results:** When pre-operative and postoperative PIRS-20, VAS, and STAI scores were compared, no significant difference was observed between group T and group S ($p>0.05$). The VAS values in group S and group T decreased significantly over time (group S: $p<0.001$; group T: $p=0.001$, respectively). The STAI scores decreased significantly over time ($p=0.001$). The PIRS-20 values remained unchanged in groups S and T ($p=0.132$, $p=0.828$, respectively).

**Conclusion:** The results of the study showed that while the type of anesthesia did not affect the quality of sleep in the group of patients receiving posterior instrumentation, the surgical procedure did influence pain reduction in both anesthesia methods.

**Keywords:** Posterior instrumentation, sleep quality, anesthetics, spine surgery

## Introduction

Sleep is necessary to improve learning, memory, and physiological functions, and deterioration of sleep quality harms quality of life. Sleep disorders can also lead to diseases such as cardiovascular disease, diabetes, and cancer. Moreover, sleep quality is associated with life expectancy, especially in older populations (1). Previous research has shown that the quality of sleep for individuals with spinal disorders is lower than that of individuals without spinal disorders. Elderly patients with degenerative lumbar spinal stenosis (LSS) may experience sleep disorders due to pain and poor sleep quality (2). In patients with knee arthritis and other musculoskeletal diseases, sleep quality is often reduced due to diminished joint strength in the resting position. In contrast, patients with LSS have increased pain in positions that significantly narrow the spinal canal, such as sleeping, which causes poor sleep quality (3). Therefore, in patients with LSS, the pain and associated sleep disorders improve after treatment. The surgical treatment of back pain improves the symptoms of post-operative pain and sleep disturbance (4). Postoperative pain and anxiety have also been found to be risk factors associated with postoperative sleep disorders. Post-surgical insomnia can lead to delayed surgical recovery, cognitive dysfunction, increased post-operative sensitivity to pain, and cardiovascular events (5). It is important for healthcare providers to address and manage post-surgical insomnia to optimize patient outcomes.

Anesthetic agents can cause sleep disorders in the postoperative process. Anesthetic drugs interrupt the rhythm of sleep and wakefulness and various biological cycles, such as body temperature and melatonin release, resulting in inadequate sleep and poor sleep quality (6). Total intravenous anesthesia (TIVA) is commonly used in spinal surgery

**Address for Correspondence:** Selcan Akesen Assoc. Prof., MD, Bursa Uludağ University Faculty of Medicine, Department of Anesthesiology and Reanimation, Bursa, Türkiye
**E-mail:** selcanakesen@uludag.edu.tr **ORCID ID:** orcid.org/0000-0002-9518-541X

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because inhalation anesthetics lower the amplitude of motor-stimulated potential, which is a key way to monitor patients during surgery. For propofol-based TIVA, remifentanil is frequently used as an additional medication. The combination of propofol and remifentanil works synergistically to achieve the desired hypnotic-analgesic effect while promoting rapid postoperative recovery. Propofol reduces intraoperative remifentanil requirements, whereas remifentanil facilitates the recovery of consciousness (7). Additionally, it has been suggested that remifentanil may indirectly improve sleep quality by enhancing the effects of propofol.

Steinmetz et al. (8) conducted a study involving 39 infants undergoing cleft lip and palate surgery to evaluate the effects of propofol, remifentanil, and fentanyl-sevoflurane on postoperative sleep disturbances. The findings indicated that while all three anesthetic regimens negatively impacted sleep quality, sevoflurane was associated with fewer postoperative sleep disturbances compared to the propofol-remifentanil combination.

The aim of this study is to evaluate, using the Pittsburgh Insomnia Rating Scale-20 (PIRS-20), the impact of the anesthesia method and surgical procedure on the sleep patterns and sleep quality of patients undergoing posterior spinal instrumentation.

## Methods

After obtaining oral and written informed consent and the study was approved by the Clinical Research Ethics Committee of Bursa Uludağ University, Faculty of Medicine (approval no: 2022-12/10, date: 08.06.2022), a total of 40 patients American Society of Anesthesiology I-III, aged 18 and over, who underwent elective spinal posterior instrumentation were included. After obtaining written and oral approvals demographic data were recorded.

The patients were divided randomly into two groups, those with sevoflurane anesthesia and those with TIVA, using the closed envelope method. Patients were evaluated before and after the surgery for sleep quality with the PIRS-20 (one month before surgery and 7$^{th}$ day postoperatively), for pain score with the Visual Analog Scale [(VAS) recorded one night before surgery and first hour postoperatively] and for anxiety score with the State-Trait Anxiety Inventory (STAI) (recorded one night before surgery and 7$^{th}$ day postoperatively).

The anesthesiologist, who recorded all the assessments, was blinded to the patient's anesthesia method. As part of the standard procedure for spinal posterior instrumentation surgery, patients were monitored in the operating room with electrocardiography, invasive or non-invasive blood pressure measurements, peripheral oxygen saturation and capnography. The administered anesthetic and analgesic agents were recorded, along with changes in the patient's blood pressure, including hypotension, and hypertension. All patients were extubated and awakened in the operating room.

The Psychiatric Clinic at the University of Pittsburgh developed the PIRS-20 scale to evaluate people's recent sleep patterns. Overall, the scale consists of 20 items across subjective sleep quality, sleep latency, sleep duration, usual sleep patterns, and sleep disorders. The score is from 0 to 60, with 20 or more points indicating poor sleep quality; the higher the score, the poorer the quality of sleep. PIRS-20 was preferred in our study because it evaluates the level of anxiety or stress-based arousal before falling asleep. Postoperative pain was assessed using the VAS on the preoperative night and the first postoperative hour. A morphine infusion was initiated using patient-controlled analgesia based on the following protocol: a total solution volume of 100 mL with a concentration of 1 mg/mL, a bolus dose of 2 mg, a lockout interval of 15 minutes, no basal infusion, and a maximum dose of 10 mg over 4 hours. In cases of nausea and vomiting, 4 mg ondansetron (Kemoset®, Deva İlaç) was administered IV.

### Management of General Anesthesia

After the patients were transferred to the operating room, an 18-gauge peripheral venous cannula was meticulously placed to establish venous access. A 0.9% sodium chloride IV infusion was started at a rate of 10 mL//kg/hour. Throughout the procedure, patients underwent continuous monitoring using pulse oximetry, electrocardiography, and non-invasive or invasive blood pressure measurements, and bispectral index (BIS). Midazolam was administered at a premedication dosage of 0.02 mg/kg. Following preoxygenation, anesthesia was induced with an intravenous injection of Propofol-PF® 1% (POLIFARMA Pharmaceuticals, Tekirdağ, Türkiye) (2 mg/kg), rocuronium (0.6 mg/kg) and fentanyl (2 mcg/kg). After securing the airway with a cuffed endotracheal tube (manufactured by Henan Tuoren Medical Device Ltd., Henan, China), mechanical ventilation was initiated with an inspired oxygen fraction of 50%, and minute ventilation was adjusted to maintain end-tidal carbon dioxide ($EtCO_2$) levels within the range of 35-45 mmHg. Group S received sevoflurane (Sevorane® liquid 100%, AbbVie Pharmaceuticals, İstanbul, Türkiye) for anesthesia maintenance, with an end-tidal sevoflurane concentration set at 1 minimal alveolar concentration. Furthermore, remifentanil (Opiva vial®, Tüm Ekip Pharmaceuticals Inc., İstanbul, Türkiye) was administered IV, at an infusion rate ranging from 0.05 to 0.2 µg kg/minimum (min). Group P received propofol at a dosage of 75-100 µg/kg/min and remifentanil IV at a dosage of 0.05-0.2 µg/kg/min.

The depth of anesthesia was monitored by maintaining BIS readings within the range of 40 to 60. The researchers ensured that the mean arterial pressure remained within a range of 20% of the initial value.

### Sample Size Estimation

The primary outcome was the postoperative PIRS-20 score. Results from a previous study 9 determined the number of patients needed for analysis using G* Power 3 (Heinrich-Heine-Universitat Düsseldorf, Germany). The Pittsburgh Sleep Quality index (PSQI) scores in the TIVA groups and inhalation groups were 12.06 (2.18) and 14.03 (1.72), respectively, in the previous study. The sample size was determined using a power of 85% and an alpha of 0.05. It was found that 19 patients in each group, totaling 38 patients, were needed to produce statistically significant results.

### Statistical Analysis

The SPSS Version 25.0 was used for statistical analysis. Frequency tables were calculated for categorical variables, and descriptive statistics were calculated for continuous variables. A Pearson chi-square test was used to examine categorical data across groups. The normal distribution of continuous variables was analyzed with the Shapiro-Wilk normality test. When the normal distribution was present, the t-test was used for two independent groups, and when there was no normal distribution, the Mann-Whitney U test was used. When there was no normal distribution, the Friedman test was used to compare measurements taken at different times in independent groups. The significance level was taken as 0.05 in all hypothesis tests.

## Results

A total of 40 patients were recruited for posterior spinal instrumentation surgery evaluation, with surgery for two patients briefly canceled. Ultimately, 38 patients were included in the whole study, with 17 in group P and 21 in group S. The consort flow diagram of patients (Figure 1) compares the patients' demographic and physiological characteristics between the two groups.

There were no significant differences between the two groups in terms of age, sex, body mass index, neck thickness, snoring, sleep apnea (witnessed), large tongue, surgical type, surgical level, and presence of decompression ($p>0.05$). The Mallampati scores were significantly different ($p=0.029$) (Table 1).

No significant difference was observed in the pre-operative and postoperative PIRS-20, VAS, and STAI scores between group T and group S ($p>0.05$). The VAS values in group S and group T decreased significantly over time ($p<0.001$, $p=0.001$, respectively). The STAI scores decreased significantly over time ($p=0.001$, $p=0.001$, respectively). The PIRS-20 values remained unchanged in groups S and T ($p=0.132$, $p=0.828$, respectively) (Tables 2-4; Figure 2).

## Discussion

The findings of this study indicated that the choice of anesthesia method had no impact on postoperative pain quality, sleep quality, or the incidence of insomnia. However, significant variations in pain and anxiety levels were observed between the preoperative and postoperative periods. Moreover, patients in this study experienced comparable changes in sleep quality both in the month leading up to the surgery and throughout the seven-day postoperative period.

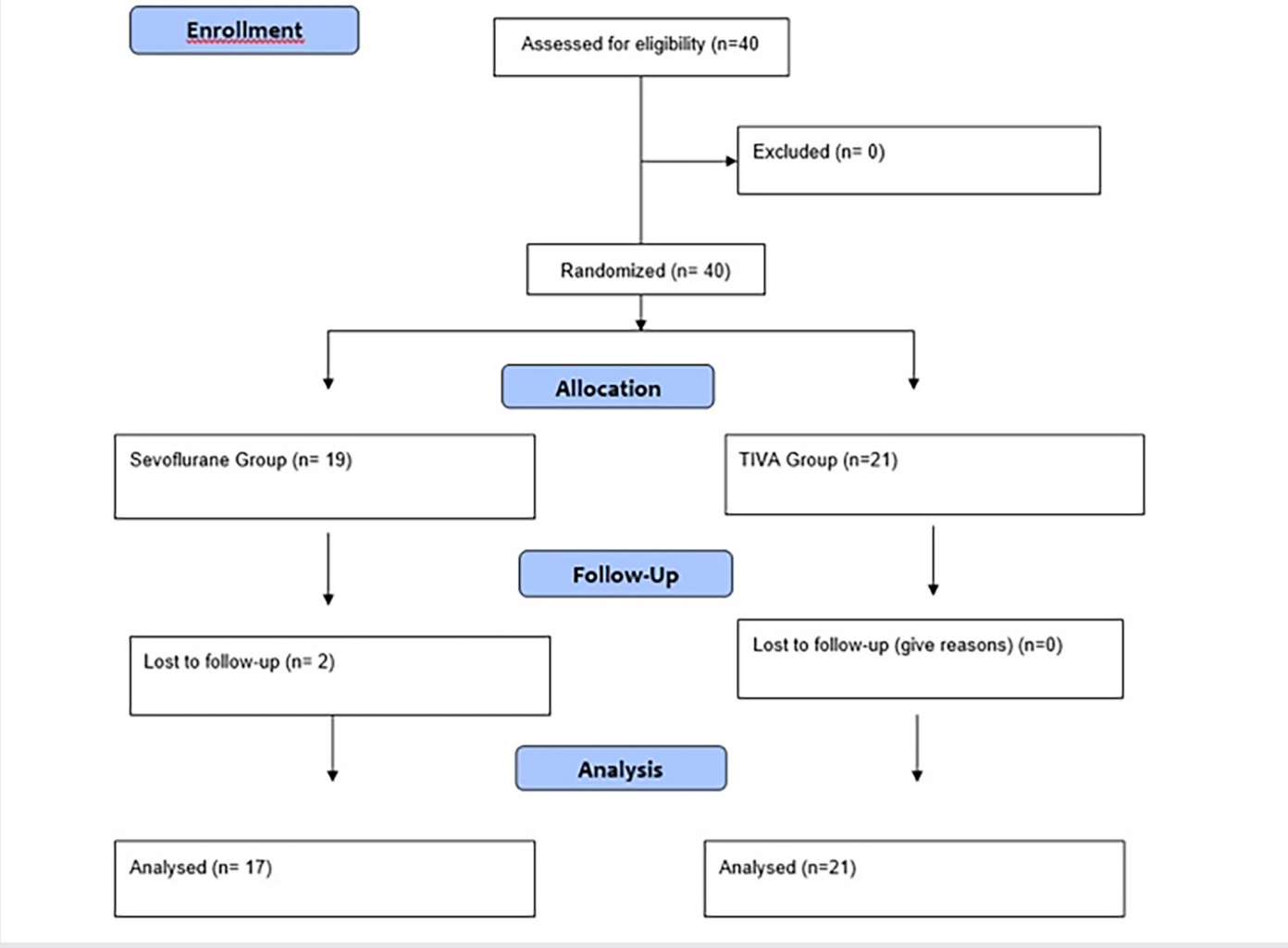



**Figure 1.** The CONSORT flow diagram of patients

**Table 1. Demographic and physiological characteristics data**

| | Group S (n=17) | Group T (n=21) | p |
|---|---|---|---|
| Age (year) | 60.76±10.10 | 55.471±9.3 | 0.581 |
| Sex (F/M) | 11/6 | 16/5 | 0.561 |
| BMI (kg/m$^2$) | 29.14±5.48 | 27.74±4.84 | 0.504 |
| ASA score (I/II/III) | 2/12/3 | 5/14/2 | 0.383 |
| Sleep disorder (Y/N) | 6/11 | 5/16 | 0.728 |
| Neck (N/T) | 5/12 | 13/8 | 0.089 |
| Mallampati (I/II/III/IV) | 1/9/6/1 | 6/13/1/1 | 0.029* |
| Snoring (Y/N) | 11/6 | 7/14 | 0.101 |
| Sleep apnea (Y/N) | 1/16 | 1/20 | 0.954 |
| Large tongue(Y/N) | 5/12 | 5/16 | 0.772 |
| Surgery (primer/ revision) | 14/3 | 19/2 | 0.685 |
| Surgery level | 16/1/0 | 10/1/10 | 0.1 |
| Dekomprestion (Y/N) | 15/2 | 16/5 | 0.542 |

*p<0.05 is significantly different, F: Female, M: Male, Y: Yes, N: No, N: Normally, T: Thickness, ASA: American Society of Anesthesiology, BMI: Body mass index

**Table 2. VAS scores**

| | Group S (n=17) | Group T (n=21) | p |
|---|---|---|---|
| PreopVAS | 5.88±.65 | 5.61±2.51 | 0.136 |
| PostopVAS | 1.47±1.28 | 2.28±1.55 | 0.101 |
| p | <0.001* | 0.001* | |

*p<0.05 is significantly different, VAS: Visual Analogue Scale

**Table 3. STAI scores**

| | Group S (n=17) | Group T (n=21) | p |
|---|---|---|---|
| STAI 1 | 41.05±8.39 | 41.33±10.57 | 0.67 |
| STAI 2 | 30.76±5.25 | 34.04±8.44 | 0.41 |
| p | 0.001* | 0.001* | |

*p<0.05 is significantly different, STAI: State-Trait Anxiety Inventory

**Table 4. PIRS-20 scores**

| | Group S (n=17) | Group T (n=21) | p |
|---|---|---|---|
| PIRS-20 1 | 17.52±12.4 | 19.38±12.898 | 0.681 |
| PIRS-20 2 | 15.11±10.54 | 18.57±13.02 | 0.471 |
| p | 0.132 | 0.828 | |

*p<0.05 is significantly different, PIRS-20: Pittsburgh Insomnia Rating Scale-20

In a study by Lee et al. (10), 63.5% of patients with symptomatic LSS experienced poor sleep quality, and other reports have linked inadequate sleep quality to certain musculoskeletal conditions. People who suffer from chronic low back pain are more likely to report getting little sleep, according to research by Marty et al. (11). Although sleep disturbances have become increasingly common, it remains unclear whether LSS is the primary underlying cause of this issue. Nevertheless, given the much higher incidence of neuropathic pain in the group of poor sleepers, neuropathic pain may mediate the relationship between LSS and sleep disturbance (11). This finding aligns with previous studies

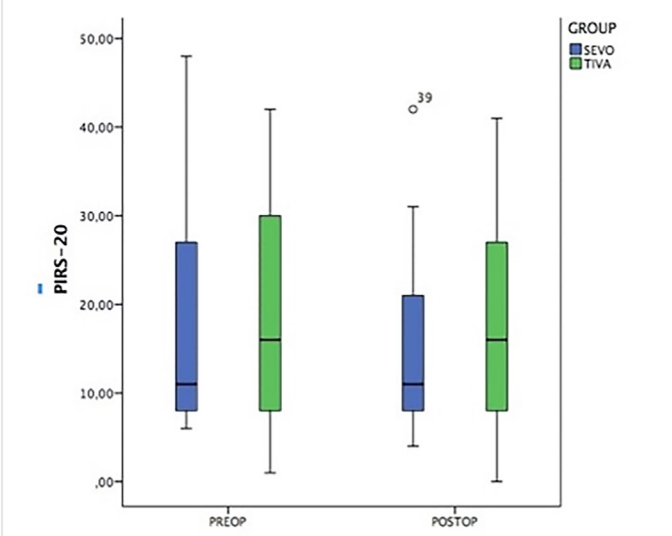



**Figure 2.** Comparison of PIRS-20 score according to groups

demonstrating a correlation between neuropathic pain and sleep disturbances. Furthermore, the improvement in sleep quality following surgery provides additional insight into the relationship between LSS and impaired sleep (12).

Kim et al. (13) found that treating LSS patients surgically or conservatively improved their sleep quality, as measured by the patients' PSQI. Surgery led to faster sleep quality improvement, and the surgical group experienced lower insomnia, sleep disorder, and daytime dysfunction than the conservative treatment group. In addition, patients in the surgical group showed a continuous improvement in their quality of sleep after surgery. This study showed a significant improvement in pain scores and quality of sleep after surgical treatment. The type of anesthetic used appears to have an impact on the incidence of postoperative pain.

In a study by Meng et al. (14), the pain and quality recovery scores of groups receiving TIVA and Sevoflurane were compared. The results showed that the sevoflurane group had higher VAS values, but the TIVA group had a superior quality of recovery. Propofol is a frequently used IV anesthetic medication for both starting and maintaining general anesthesia. An improved wake-up experience and less nausea and vomiting are two of the many advantages of using TIVA with propofol (15). Propofol can ease pain and has been shown in animal studies to lower levels of cytokines that cause inflammation and prevent N-methyl-D-aspartate (NMDA) receptors from activating (16,17). Clinical trials comparing propofol to inhalational anesthesia demonstrated that propofol offered superior results, and pain levels decreased during the 24 hours following surgical procedures (18). In addition, the use of TIVA in combination with propofol may decrease the occurrence of chronic postsurgical pain (19). Nevertheless, other clinical investigations have shown no superior analgesic efficacy following surgical intervention with propofol. The efficacy of propofol as an analgesic may vary depending on surgical procedures, as the severity and mechanism of pain are likely to change across various types of surgeries, which aligns with the notion of intervention-specific analgesia (20,21). Additionally, the

administration of propofol has been found to mitigate the hyperalgesic effects induced by remifentanil infusion.

One important matter is how propofol blocks NMDA receptors, which are involved in the pathways through which remifentanil provides analgesia (16). In our study, there was no difference between the postoperative pain values for the inhalation group and the TIVA group. Our patients likely experienced high levels of preoperative pain due to spinal stenosis, and the postoperative reduction in pain may explain the lack of distinction between anesthesia methods. Hu et al. (22) conducted a study using the PSQI to assess sleep quality following a laparoscopic gynecologic procedure in females with insomnia who were under TIVA anesthesia. This study had the potential to assess the effect of gender and surgical methods on the quality of sleep following surgery. However, the study found a statistically significant improvement in sleep quality in patients who underwent TIVA anesthesia compared to sevoflurane anesthesia. Another study found that sevoflurane has a less enduring effect on sleep quality than propofol (8).

However, Ma et al. (23) presented a different perspective. The PSQI uses a threshold of 6 points to indicate the presence of sleep problems. As the PSQI score increases, sleep quality declines. Ma et al. (23) study found that the PSQI scores at 24 and 48 hours post-surgery were greater than 6 and higher than the pre-surgery values in both groups, showing the presence of postoperative sleep disturbances. Nevertheless, no significant difference was reported between the TIVA and inhalation groups. This study showed that the quality of sleep before and after surgery was different for all patients. However, comparing the methods of anesthesia, the PIRS-20 scores were similar between the TIVA and inhalation groups, and there was no significant difference in sleep quality.

### Study Limitations

The present study was carried out in a group of patients whose low sleep quality was due to pain and in whom surgery could make a significant difference. It can pose a problem in investigating the difference between anesthetic agents and can be regarded as a limitation of the study. On the other hand, it is important to investigate the effect of different anesthetic agents on sleep quality in patients with preoperative insomnia. One of the significant limitations of our study is that all patients had pain, and it is not known whether there was any sleep disorder before the onset of pain. The lack of a control group without pain is a deficiency. However, since surgical intervention is not applied to spine pathologies without pain, the possibility of surgical treatment is not considered.

## Conclusion

The results of the current study showed that while the type of anesthesia did not affect the quality of sleep in patients receiving posterior instrumentation, the surgical procedure affect pain reduction in both anesthesia methods.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of Bursa Uludağ University, Faculty of Medicine (approval no: 2022-12/10, date: 08.06.2022).

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

### Footnotes

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

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

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# A Novel Tool for the Evaluation of Residency Training: Scale Development and Validation

Nazan Karaoğlu[1], Ümmü Doğan[2], Aşir Genç[3], Nur Demirbaş[1], Fatih Yılmaz[4], Hatice Küçükceran[1], Fatma Gökşin Cihan[1], Ümran Münire Kahraman[5]

[1]Necmettin Erbakan University Faculty of Medicine, Department of Family Medicine, Konya, Türkiye
[2]Hasköy Public Hospital, Clinic of Family Medicine, Muş, Türkiye
[3]Necmettin Erbakan University Faculty of Science, Department of Statistics, Konya, Türkiye
[4]Ministry of National Education, Konya, Türkiye
[5]Necmettin Erbakan University Faculty of Political Science, Department of Business Management, Konya, Türkiye

## ABSTRACT

**Introduction:** The purpose of medical specialty training is to provide the physician with sufficient knowledge, skills, attitudes, and qualifications in the chosen field of medicine. In medical training, communication and social opportunities are crucial as well as appropriate goals, programs, and learning environments. The purpose of this paper is to develop a valid and reliable measurement tool to evaluate the compliance of this training with the standards.

**Methods:** In this survey-type research, in line with the literature, a draft scale to evaluate the training in both the department and the institution consisting of 49 items, was created.

**Results:** The study involved 497 residents from family medicine residency programs across Türkiye. The exploratory factor analysis revealed that the Scale for Department Evaluation of Medical Specialty Training had four factors whereas the Scale for Institution Evaluation of Medical Specialty Training had three factors. The factorial structures of both scales were confirmed by confirmatory factor analysis. The Cronbach's alpha values were 0.941 and 0.928, respectively. Moreover, both scales explain a high amount of total variance.

**Conclusion:** The Department Evaluation Scale for Medical Specialty Training, consisting of 25 items and four factors, and the Institution Evaluation Scale for Medical Specialty Training consisting of 20 items and three factors are valid and reliable tools to study medical specialty training.

**Keywords:** Departments, institutional, scale, residency, training

## Introduction

Lately, there have been various studies in the literature, indicating that medical specialty training should be a process structured within certain standards, honor and ethical principles of medicine, shaped by the needs and expectations of society, and certified by objective-based measurements and evaluations (1-3).

The World Federation for Medical Education (WFME) reports three main categories, termed the "trilogy," for quality improvement: basic medical education, postgraduate medical education, and continuing professional development (2). For post-graduate medical education WFME had eight areas to improve: which are "1. mission and values, 2. curriculum, 3. assessment, 4. postgraduate doctors, 5. teachers and clinical supervisors, 6. education and training resources, 7. quality improvement and 8. governance and administration" (2). In medical education, it is necessary to create awareness of the educational environment in the institution for both trainers and trainees, along with the content of the curriculum. How the educational environment is perceived by the trainees plays a key role in determining the quality of learning processes (4). WFME highlights the educational environment as one of the main areas for the evaluation of medical education programs (2,4-10). The Türkiye Board of Medical Specialization Curriculum Development and Standardization also defines educational environments in detail, and highlights the importance of the matter (1). However, the number of publications on how it is evaluated by the trainees is quite small (8,10-13).

The purpose of this paper is to develop a valid and reliable tool that can evaluate and measure the compliance of the education received by

**Address for Correspondence:** Hatice Küçükceran Assoc. Prof., MD, Necmettin Erbakan University Faculty of Medicine, Department of Family Medicine, Konya, Türkiye
**E-mail:** drhaticeran@gmail.com **ORCID ID:** orcid.org/0000-0002-0581-9934

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family medicine specialty students with the standards, the educational and social opportunities, the administrative processes, and the training environment.

## Methods

**Type of research:** Since the purpose of this research is to develop a measurement tool to evaluate the training received by family medicine specialty students, it qualifies as survey research.

**The population and sample:** the study population consists of family medicine residents who use the internet and social media and are receiving family medicine specialty training in Türkiye on account of the widespread use of social media, the large number of groups involving residents and the chance to reach more participants, the researchers decided to collect the data through the internet.

As the literature recommends that the sample size be at least 10 times the number of questions in the scale, the researchers aimed to reach 490 participants (14). The researchers adopted the convenience sampling method and shared the link to the questionnaire, which briefly contained the research purpose and was created using "Google Docs," on "WhatsApp, Gmail, and Yahoo" groups. Those who followed the link and answered the questions were accepted as voluntary participants.

**Ethics statement:** Ethical approval was granted by Necmettin Erbakan University, Non-Interventional Clinical Research Ethics Committee (approval number: 2023/4720, date: 15/12/2023). This research was carried out in line with the Declaration of Helsinki. All participants were informed about the research and confirmed that they voluntarily participated in the research.

**Data collection tools:** The researchers created an item pool of 49 statements inspired by a practitioner tool used in a published thesis, main topics of national and international recommendations, and similar studies (1-3,8,9,11-13,15-17). The internal consistency coefficient of the questionnaire used in the abovementioned thesis was found to be $\alpha$=0.940 for the departmental evaluation, and $\alpha$=0.952 for the institutional evaluation in the specialty training; and it was considered to have high reliability (13).

The questionnaire used in this research consists of three sections. The first one collects the socio-demographic information of the participants, the second evaluates training in the department, and the third evaluates training in the institution as noted below in more detail:

**Medical specialty training-department evaluation scale:** This section has 25 items about the department in which the resident is receiving specialty training, including the conformity of the training to the standards, training opportunities, social relations in the department, qualifications of the trainers, training environment and academic development. The five-point Likert scale has "1- never, 2- rarely, 3- sometimes, 4- often, 5- always" response options indicating the level of agreement with the statements, has no reverse-coded items.

**Medical specialty training-institution evaluation scale:** This section has 24 items related to interpersonal relations, social facilities, and the educational environment of the institution in which the resident receives specialty training. The five-point Likert scale has "1- never 2- rarely, 3- sometimes, 4- often, 5- always" response options indicating the level of agreement with the statements, and has no reverse-coded items.

### Statistical Analysis

The researchers used IBM SPSS AMOS (Version 23) in the data analysis. Exploratory and confirmatory factor analyses for construct validity, and Cronbach's Alpha coefficient to check internal consistency were used and explained in detail in the results section.

## Results

With an average age of 29.08±4.1 years, 497 specialty students participated in this research. Among the participants, 70.21% (n=349) were females, 57.33% (n=285) were married, and 30.2% (n=150) had children. 71.4% (n=355) of the participants were satisfied with their city of residence, and 65.24% (n=324) were satisfied with their chosen specialty. The median order of preference for family medicine in the medical specialty exam was 2 (1-57), and 60.91% (n=303) of the participants stated that they would choose family medicine again if they had a second chance.

### Medical Specialty Training-Analysis of Department Evaluation Scale

### Construct Validity

The researchers employed exploratory and confirmatory factor analyses for construct validity. Kaiser-Meyer-Olkin (KMO) and Bartlett's tests were used to assess whether the data gathered during the pilot study were suitable for factor analysis. The results indicated that the KMO value (0.943) is acceptable (KMO >0.50), which means that the data is suitable for factor analysis (18). The results of Bartlett's test showed that there are significant relationships between the variables and the data are suitable for factor analysis [$\chi^2$: 6587.550; standard deviation (SD): 300; $p<0.001$].

### The Exploratory Factor Analysis (EFA)

In the analysis, the researchers used varimax rotation. As a consequence, 25 items with eigenvalues greater than 1.0 were grouped under four factors, explaining 58.68% of the total variance. This value is acceptable according to the literature (19). The factor loadings above 0.30 are acceptable, as the findings show that they exceed this threshold (20,21). Eigenvalues, factor loadings, and the total variance explained are shown in Table 1. As a result of the analysis, the researchers identified the factors related to the departmental evaluation of medical specialty training, taking the items and the relevant literature into account. Accordingly, they called the factors "training" items (1-9), "communication" items (10-18), "scientific activities" items (19-23), and "assessment and evaluation" items (24,25).

### The Confirmatory Factor Analysis (CFA)

To confirm the factorial structure, the researchers performed a confirmatory factor analysis. The correlation matrix in Table 2 indicates that the highest correlation is between the "training" and "communication" factors (r=0.781). The path diagram of the scale is given in Figure 1. Moreover, fit indices indicate a good fit to the factorial structure. [$\chi^2$=756.436, df=260, $\chi^2$/df=2.909 root mean square error

of approximation (RMSEA)=0.062, comparative fit index (CFI)=0.923, goodness of fit index (GFI)=0.893, tucker-lewis index (TLI)=0.911 adjusted GFI (AGFI)=0.866] (21-23).

### Internal Consistency

The researchers adopted Cronbach's Alpha coefficient to check internal consistency. The coefficients for the factors of the scale are 0.895 for the "training" factor; 0.890 for the "communication" factor; 0.871 for the "scientific activities" factor; and 0.705 for the "assessment and evaluation" factor. As for the whole scale, it is 0.941 (Table 1). Accordingly, the scale is highly reliable (24).

### Medical Specialty Training-Analysis of Institution Evaluation Scale

### Construct Validity

The construct validity of the scale was tested using exploratory and confirmatory factor analyses. To check whether the data are suitable for factor analysis, the researchers employed KMO and Bartlett's tests. The results indicated that the KMO value (0.935) is acceptable (KMO >0.50), which means that the data are suitable for factor analysis (18). The results of the Bartlett's test also showed that there are significant relationships between the variables and the data are suitable for factor analysis ($\chi^2$: 5185.997; SD: 190; $p<0.001$).

### The Exploratory Factor Analysis (EFA)

In EFA, the researchers used the varimax rotation method. They included 24 items in the analysis, although some of them (items 26, 32, 33, 46) were excluded from the analysis since they had high factor loadings on more than one factor with loading differences below 0.10 (25,26). As a consequence, 20 items, with eigenvalues greater than 1.00, were grouped into three factors explaining 57.94% of the total variance. Eigenvalues, factor loadings, and the total variance explained are shown in Table 3.

As a result of the analysis, the researchers identified factors related to the

**Table 1. The medical specialty training department evaluation scale-EFA and reliability analysis results**

| Variable | Factor load | Eigenvalue | Variance (%) | Cronbach's alpha | Corrected item-total correlation |
|---|---|---|---|---|---|
| **Training** | | 10.613 | 42.451 | 0.895 | |
| SB3 | 0.743 | | | | 0.743 |
| SB4 | 0.741 | | | | 0.701 |
| SB2 | 0.728 | | | | 0.706 |
| SB1 | 0.725 | | | | 0.701 |
| SB13 | 0.616 | | | | 0.664 |
| SB12 | 0.605 | | | | 0.672 |
| SB8 | 0.599 | | | | 0.558 |
| SB9 | 0.597 | | | | 0.646 |
| SB25 | 0.540 | | | | 0.546 |
| **Communication** | | 1.492 | 5.969 | 0.890 | |
| SB6 | 0.713 | | | | 0.647 |
| SB19 | 0.704 | | | | 0.672 |
| SB21 | 0.648 | | | | 0.740 |
| SB5 | 0.634 | | | | 0.603 |
| SB23 | 0.627 | | | | 0.747 |
| SB7 | 0.591 | | | | 0.563 |
| SB20 | 0.556 | | | | 0.628 |
| SB24 | 0.528 | | | | 0.593 |
| SB22 | 0.502 | | | | 0.634 |
| **Scientific activities** | | 1.333 | 5.333 | 0.817 | |
| SB17 | 0.767 | | | | 0.609 |
| SB16 | 0.766 | | | | 0.584 |
| SB18 | 0.560 | | | | 0.599 |
| SB14 | 0.557 | | | | 0.631 |
| SB15 | 0.556 | | | | 0.623 |
| **Assessment and evaluation** | | 1.233 | 4.932 | 0.705 | |
| SB10 | 0.799 | | | | 0.545 |
| SB11 | 0.795 | | | | 0.545 |
| **Total** | | | 58.685 | 0.941 | |

institutional evaluation of medical specialty training, taking the items and the relevant literature into account (2). Consequently, they called the factors "environment-relationships" items (1-9), "social facilities" items (10-15), and "training environment" items (16-20).

### The Confirmatory Factor Analysis (CFA)

To confirm the factorial structure, the researchers did a confirmatory factor analysis. The correlation matrix in Table 4 indicates that the highest correlation is between the "training environment" and "social facilities" factors (r=0.572). The path diagram of the scale is given in Figure 2. In addition, the fit indices to the factorial structure indicate that there is a good fit. ($\chi^2$=539.211; df=161; $\chi^2$/df=3.349; RMSEA=0.069; CFI=0.925; GFI=0.903; TLI=0.912; AGFI=0.873) (21-23).

### The Internal Consistency

The alpha coefficients for the factors of the scale are 0.905 for the "environment-relationships" factor, 0.786 for the "social facilities" factor, and 0.837 for the "training environment" factor. Regarding the whole scale, the reliability coefficient is 0.928 (Table 3). In brief, the scale is highly reliable (24).

## Discussion

The effects of training processes and training environments on learning are of growing importance. The training environment can exert a positive or negative influence on student motivation. It has been asserted that a comprehensive understanding of the components of the educational environment, held by both students and trainers, can serve as a foundation for establishing arrangements that are conducive to learning objectives (4-10). Thus, the literature review indicates that several papers have studied the quality of training (7-9,11-13,15-17). However, the fact that almost none of those studies used a structured and tested scale has affected the results and generalizability of the studies, and prevented the formation of a common standard. That's why the present

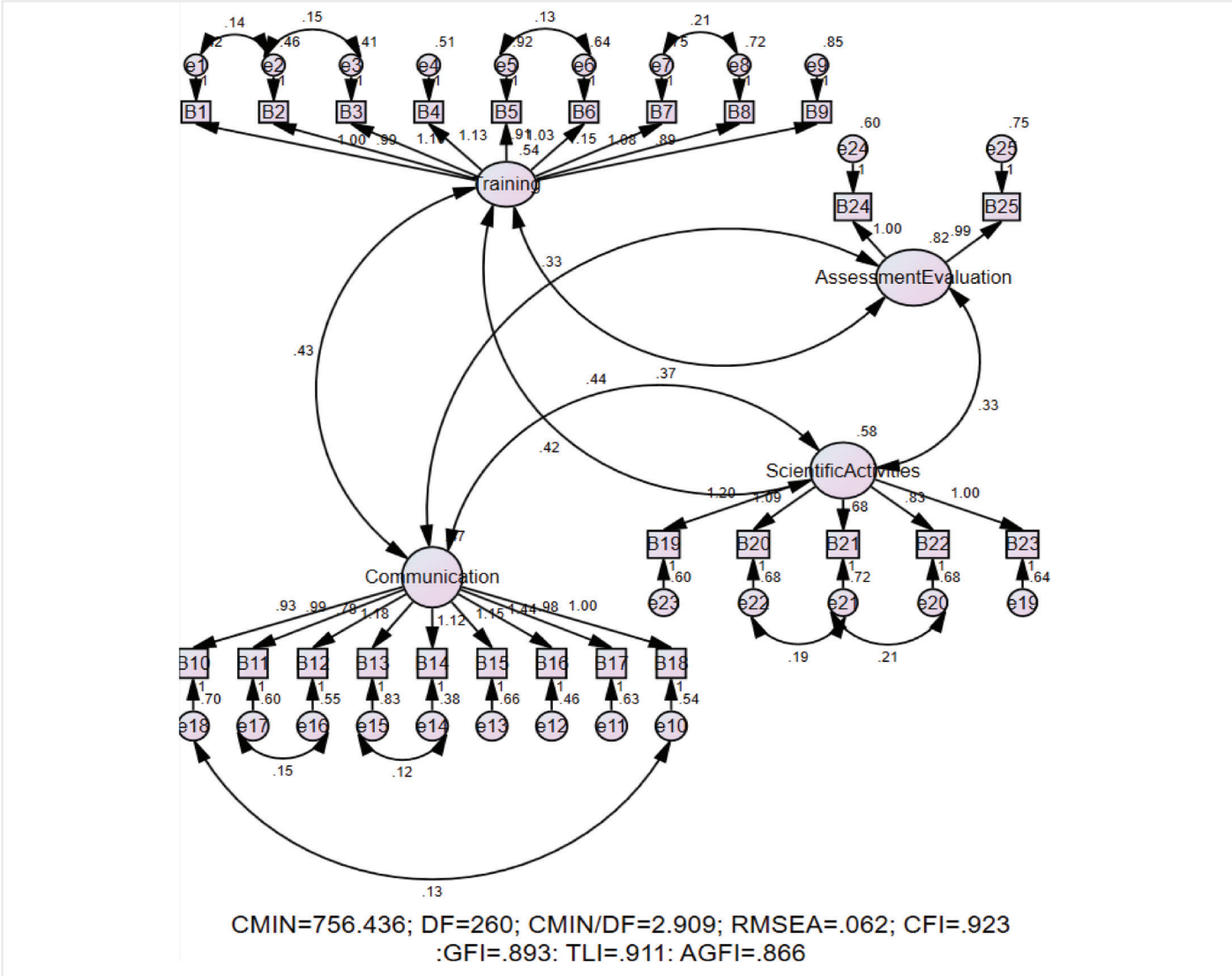



**Figure 1.** Confirmatory factor analysis for medical specialty training department evaluation scale
RMSA: Root mean square error of approximation, CFI: Comparative fit index, GFI: Goodness of fit index, TLI: Tucker-lewis index, AGFI: Adjusted goodness of fit index

study is of high importance, both nationally and internationally, as it addresses the lack of a measurement tool. In this paper, the researchers developed two scales that can be used separately or together to evaluate medical specialty training. The Medical Specialty Training Department Evaluation Scale, used to evaluate specialty training in the department, consists of 25 items and four factors. Similarly, the "Medical Specialty Training Institution Evaluation Scale" is a valid and reliable tool meant to evaluate the reflections of specialty training in the institution, consisting of 20 items and three factors.

The study involved 497 family medicine residents from educational institutions across Türkiye The data collected from family medicine residents, who are crucial in specialty training and have the opportunity to observe the training process from different perspectives due to their training rotations, are the strength of this paper. Moreover, some expressions, specific to particular medical disciplines, were omitted from the first study, thereby making the scale useful for all medical specialties. Alpha values of the measured scales are 0.941 and 0.928, respectively, which indicates high reliability.

**Table 2. Correlations between the factors of the medical specialty education department evaluation scale**

| | | Training | Communication | Scientific activities | Assessment and evaluation |
|---|---|---|---|---|---|
| **Training** | r | 1 | | | |
| **Communication** | r | 0.781** | 1 | | |
| **Scientific activities** | r | 0.763** | 0.751** | 1 | |
| **Assessment and evaluation** | r | 0.676** | 0.621** | 0.742** | 1 |

**Correlation is significant at the 0.01 level (2-tailed)

**Table 3. The medical specialty training institution evaluation scale-EFA and reliability analysis results**

| Variable | Factor load | Eigenvalue | Variance (%) | Cronbach's alpha | Corrected item-total correlation |
|---|---|---|---|---|---|
| **Environment-relationships** | | 8.620 | 43.102 | 0.914 | |
| SK4 | 0.844 | | | | 0.773 |
| SK3 | 0.829 | | | | 0.759 |
| SK5 | 0.819 | | | | 0.782 |
| SK2 | 0.703 | | | | 0.712 |
| SK9 | 0.651 | | | | 0.619 |
| SK1 | 0.615 | | | | 0.641 |
| SK8 | 0.605 | | | | 0.699 |
| SK7 | 0.599 | | | | 0.685 |
| SK6 | 0.519 | | | | 0.635 |
| **Social facilities** | | 1.672 | 8.362 | 0.786 | |
| SK11 | 0.704 | | | | 0.554 |
| SK12 | 0.683 | | | | 0.556 |
| SK10 | 0.682 | | | | 0.592 |
| SK14 | 0.578 | | | | 0.541 |
| SK15 | 0.575 | | | | 0.416 |
| SK13 | 0.509 | | | | 0.556 |
| **Training environment** | | 1.295 | 6.478 | 0.837 | |
| SK17 | 0.761 | | | | 0.641 |
| SK19 | 0.759 | | | | 0.687 |
| SK18 | 0.741 | | | | 0.626 |
| SK16 | 0.665 | | | | 0.614 |
| SK20 | 0.559 | | | | 0.625 |
| **Total** | | | 57.943 | 0.928 | |

EFA: Exploratory factor analysis

**Table 4. Correlations between the factors of the medical specialty training institution evaluation scale**

| | | Environment-relationships | Social facilities | Training environment |
|---|---|---|---|---|
| Environment-relationships | r | 1 | | |
| Social facilities | r | 0.553** | 1 | |
| Training environment | r | 0.572** | 0.390** | 1 |

**Correlation is significant at the 0.01 level (2-tailed)

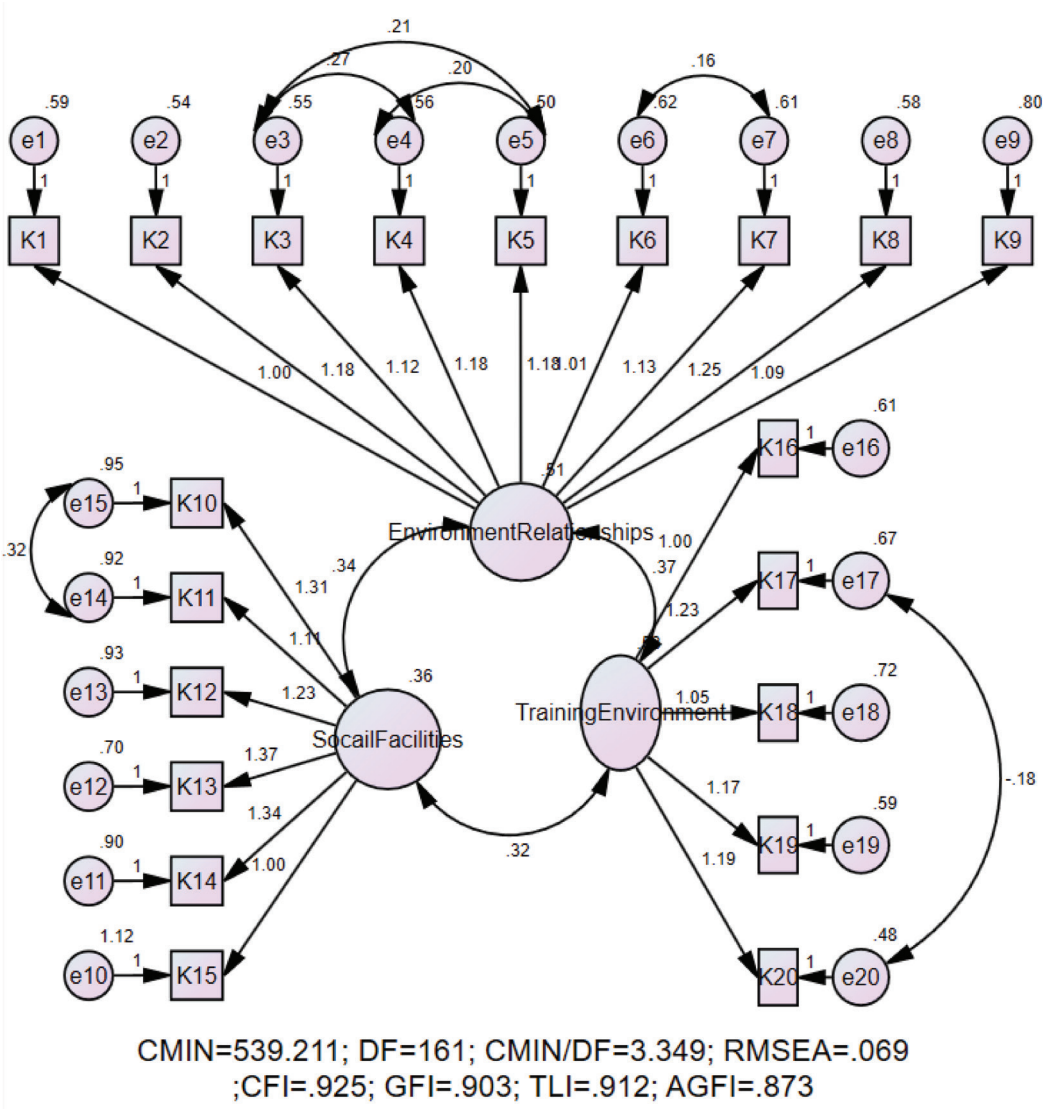



**Figure 2.** Confirmatory factor analysis for medical specialty training institution evaluation scale
RMSA: Root mean square error of approximation, CFI: Comparative fit index, GFI: Goodness of fit index, TLI: Tucker-lewis index, AGFI: Adjusted goodness of fit index

The WFME emphasizes that in postgraduate medical education it is essential to define the requirements of education and to follow a systematic educational programme that defines the general and discipline-specific components of education. However, in a limited number of studies conducted in Türkiye or in specific hospitals, residents are observed to complain about the limitations of educational and research opportunities, and that service delivery is prioritized over their education (11,12). However, one of the most basic standards set by the WFME and the Board of Specialization in Medicine Curriculum Creation and Standard Setting System (TUKMOS in Turkish), is to prioritize the education of residents and to ensure that the integration of health services is structured according to education (1,2). In fact, one study showed that residents' satisfaction with their education increased with their participation in scientific activities (17). A much larger study in Japan also found that participation in scientific activities increased satisfaction with education (27). We believe that the present study will make an important contribution to this field by providing a scale related to the quality of education, which is emphasized by both the WFME and TUKMOS, but has not yet been measured in our country with a structured data collection tool.

### Study Limitations

The voluntary participation, data collection via internet, and study population being limited to only family medicine residents may introduce bias. The scale and items developed in this study cannot be discussed in detail. This is due to the fact that there is no other scale related to the subject for comparison.

## Conclusion

In conclusion, the scales are valid and reliable, and can be used to evaluate the training received by the residents. In addition, when

the scales are used together, (department and institution) they provide a thorough evaluation. Moreover, the scales can also be used independently to eliminate the positive or negative effects of the institution on the department or vice versa. It is thought that both scales will become more effective and efficient as they are used in different fields of expertise and institutions. The scales, as used in new research, will be able to evaluate the educational processes more objectively.

### Ethics

**Ethics Committee Approval:** Ethical approval was granted by Necmettin Erbakan University, Non-Interventional Clinical Research Ethics Committee (approval number: 2023/4720, date: 15/12/2023).

**Informed Consent:** All participants were informed about the research and confirmed that they voluntarily participated in the research.

### Footnotes

**Authorship Contributions:** Concept - N.K., Ü.D., A.G., N.D., F.Y., H.K., F.G.C.; Design - N.K., Ü.D.; Data Collection or Processing - Ü.D., N.D., F.G.C.; Analysis or Interpretation - N.K., A.G., F.Y., H.K., Ü.M.K.; Literature Search - N.K., Ü.D., N.D.; Writing - N.K., Ü.D., A.G., N.D., F.Y., H.K., F.G.C., Ü.M.K.

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

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# Evaluation of Diabetic Nephropathy in Syrian Refugee Patients Admitted to the Internal Medicine Department

Ece Çiftçi Öztürk[1], Hüseyin Öztürk[2], Özge Yasun[2], Nida Halıcı Zavalsız[1], Esra Kaplan Arat[3], Onur Arat[3], Fatma Pınar Ziyadanoğlu[1], Zeynep Karaali[2]

[1]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkitye, Başakşehir Çam and Sakura City Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[3]İzmit Seka State Hospital, Clinic of Internal Medicine, Kocaeli, Türkiye

## ABSTRACT

**Introduction:** There are a total of 5,577,858 Syrian refugees worldwide as of 2020. Türkiye has the highest number of Syrian refugees. Since the beginning of migration from Syria, measures have been taken to ensure that individuals with chronic diseases receive specific treatment. Diabetic nephropathy, also known as diabetic kidney disease, is the most common cause of chronic kidney disease. This study aimed to evaluate diabetic nephropathy in Syrian immigrant patients hospitalized in our center and to compare their data with Turkish patients.

**Methods:** We included the Syrian patients who were hospitalized for any indication in University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Internal Medicine Ward. We recorded the patient's initial laboratory findings as urea, creatinine, spot urine protein creatinine ratio, and hemoglobin A1c (HbA1c).

**Results:** The study found that the number of Syrian individuals in the age group under 65 were higher than that of Turkish individuals. Among patients over 65, Turkish patients had a statistically significant higher proportion with estimated glomerular filtration rate (eGFR)>60 mL/minimum/1.73 m² compared to Syrian patients. In the group aged 65 and over, the proportion of Syrian patients with eGFR<60, was found to be higher. HbA1c was found to be higher in the Syrian group.

**Conclusion:** This study identified significant health disparities between Syrian refugees and Turkish patients, which may be attributed to the profound effects of war, forced migration, and the challenges of being a refugee. These findings highlight the long-term health consequences of displacement, limited access to healthcare, and the socioeconomic hardships faced by refugees, which may contribute to their increased burden of chronic disease. They emphasize the importance of early screening and ongoing management to prevent chronic disease progression in this vulnerable population.

**Keywords:** Diabetes, diabetic nephropathy, syrian refugees

## Introduction

Since 2011, Türkiye has hosted 3.74 million Syrian refugees and played a critical role in saving millions of Syrians who had to flee their country after the war (1). As of December 31, 2020, there were a total of 5,577,858 Syrian refugees worldwide. The total number of registered Syrians under temporary protection in Türkiye is 3,641,370. Among this population, 1,731,058 individuals (47.5%) were children aged 0-18 years. The combined number of children (aged 0-18) and women accounted for 2,581,632 individuals, representing 70.9% of the total Syrian refugees in Türkiye. According to the age distribution table published by the Migration Management, Syrian men constituted 53.9% of the total Syrian refugee population, while Syrian women comprised 46.1%. Additionally, 66,576 individuals (1.8%) were aged 65 and over, representing the elderly population within the Syrian refugee community (2).

As of December 31, 2020, the total population of Türkiye was 83,614,362, with males comprising 50.1% and females 49.9% of the population. The proportion of the population aged 15-64 years, which was 66.5% in 2007, increased to 67.7% in 2020. The proportion of the child population (0-14 years) declined from 26.4% to 22.8%, while the proportion of the population aged 65 and over rose from 7.1% to 9.5%. The total foreign population in Türkiye has reached 1,333,410. Of this population, 49.7% are male, while 50.3% are female (3).

**Address for Correspondence:** Ece Çiftçi Öztürk MD, University of Health Sciences Türkiye, İstanbul, Haseki Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
**E-mail:** eciftci3506@gmail.com **ORCID ID:** orcid.org/0000-0002-9223-4212

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In Türkiye, refugees under temporary protection status have access to public healthcare services on an equal basis with Turkish citizens. To facilitate healthcare access, interpreter services are provided, and registration procedures are expedited for certain vulnerable groups. Countries hosting large numbers of Syrian refugees, in Lebanon, primary healthcare services are provided free of charge, while in Jordan, healthcare services were initially free but became partially paid in 2014 due to increasing financial burdens. In Iraq and Egypt, healthcare services for Syrian refugees are supported by national and international organizations. While these policies aim to improve healthcare access for refugees, challenges such as language barriers, financial constraints, and the strain on healthcare systems remain significant obstacles. Refugees often face living conditions that exacerbate chronic disease risk factors, such as poor housing conditions and nutrition. Chronic diseases are prevalent among urban refugees in the Middle East, with rates ranging from 9% to 50%. Hypertension and diabetes are some of the most common chronic diseases contributing to morbidity and mortality within this population (4). A meta-analysis conducted between 2011 and 2021, which included 466 centers and 237,723 Syrian refugees, found a prevalence of 12% for type 2 diabetes mellitus, 24% for hypertension, 5% for cardiovascular diseases, 4% for chronic respiratory diseases, and 11% for arthritis (5). In Türkiye, hypertension affects 31.2% of the adult population as of 2021 (6). According to the latest data from the International Diabetes Federation, 16 in every 100 individuals in Türkiye are affected by diabetes, and there are 9,020,900 adult diabetes cases (7). A 2019 survey conducted on 10,019 Syrian refugees in Türkiye found that 15.2% of participants reported having a chronic disease, with the most commonly reported conditions being hypertension, psychiatric disorders, and diabetes (8). Furthermore, a study indicated that more than 50% of Syrian refugees in Türkiye are at high risk of developing chronic diseases (9).

Deaths from chronic diseases are responsible for nearly half of global mortality, with cardiovascular diseases, obesity, and diabetes playing significant roles. Among preventable chronic diseases, diabetes has become an increasingly important health issue worldwide due to its rising prevalence and associated complications. Approximately 537 million people worldwide have diabetes. The number of people with diabetes is projected to rise to 643 million by 2030 (10). Diabetic nephropathy (DN) is one of the chronic microvascular complications of diabetes and is characterized by progressive decline in estimated glomerular filtration rate (eGFR) and albuminuria.

Since the migration from Syria, efforts have been made to provide emergency health services for individuals with chronic diseases, ensure access to regular health care services (such as outpatient clinics and hospital admissions), and provide essential medications, as well as treatments like hemodialysis and chemotherapy. These efforts have led to the accumulation of experience and knowledge at various levels in health centers. Our hospital, located in the Aksaray district of Fatih, İstanbul, an area with a high concentration of refugee populations, has been at the forefront of these efforts. This study aims to evaluate DN in Syrian migrant patients admitted to our hospital's Internal Medicine Department and to compare these patients with Turkish citizens. Through comprehensive statistical analysis of our data, we aim to provide a pioneering evaluation of diabetes and DN in a population with the highest refugee concentration, studied at a third-level hospital. Based on the available literature, this is the first study to focus on this critical issue.

## Methods

Our study is a retrospective, analytical, cross-sectional, single-center observational study approved by the Health Sciences University. This study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (approval number: 2020-227, date: 23.12.2020) and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. The study included Syrian-origin patients aged 15 years and older, who were admitted to the Internal Medicine Department of Health Sciences University, Haseki Training and Research Hospital between September 16, 2011, and January 1, 2018. In total, 950 patients were included in the study. The study population consisted of 483 patients, excluding-repeat admissions. For the control group, 467 Turkish patients were selected from those who were admitted to the same healthcare institution within the same time period and whose hospitalization occurred immediately after the Syrian-origin patient's protocol number was assigned. Data were collected from patient records, including protocol number, gender, age, and laboratory results obtained from initial admissions, such as urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), spot urine protein/creatinine ratio, and hemoglobin A1c (HbA1c) levels.

eGFR was calculated using the MDRD equation (Isotope Dilution Mass Spectrometry) with the Statistical Package for the Social Sciences (SPSS) 22.0. Biochemical tests (urea, creatinine) were performed using the UniCel AU2700® Chemistry Analyzer, while HbA1c tests were measured using the UniCel DxI 800 Access Immunoassay System. Descriptive analyses were conducted based on current guidelines, with diseases being categorized. Kidney damage staging was done according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (11). Proteinuria levels were determined using the spot urine protein/creatinine ratio (12).

The primary endpoint of our study was to investigate the differences in demographic characteristics between Syrian and Turkish patients. The secondary endpoint focused on the analysis of patients with HbA1c>6.5, eGFR <60 mL/minimum (min.)/1.73 m, and comparing the differences between these groups.

### Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows. Descriptive statistics for categorical variables were presented as frequencies and percentages, while numerical variables were expressed as means, standard deviations, and medians (interquartile range 25-75). For the comparison of categorical variables, the chi-square test was used, and for the comparison of continuous variables, the Mann-Whitney U test was used. Statistical significance was taken as $p<0.05$.

## Results

The mean age of Syrian patients was statistically significantly lower than that of Turkish patients (p<0.001). There was no significant difference in gender distribution (p=0.064; Table 1).

The study found that the proportion of Syrian individuals in the age group under 65 was higher than that of Turkish individuals, while the proportion of Turkish individuals was higher among those aged 65 and older (Table 2). Examining the distribution by age groups, revealed that Syrian individuals were represented at a higher rate in the 20-29 age group compared to Turkish individuals (20.1% vs. 5.4%). For the 30-49 and 50-59 age ranges, the distribution was relatively similar between the two groups. However, in age groups of 60 and above, Turkish individuals were represented at progressively higher rates, with a particularly notable increase in the 70 and older group (38.3% for Turkish patients compared to 15.7% for Syrian patients); a significant statistical difference was found. (p<0.001) (Table 3) (Figure 1).

Among the population under 65, no significant difference was observed in renal function (eGFR-based) between Turkish and Syrian patients (p=0.667, p=0.065). However, among patients over 65, Turkish patients had a statistically significant higher proportion with eGFR>60 mL/min/1.73 m² compared to Syrian patients. In the group aged 65 and over, the proportion of Syrian patients with eGFR<60 was found to be higher, but this difference was not statistically significant (p=0.065) (Table 4).

**Table 1. Analysis of age and gender data of patients**

| Total (n=950) | | Turkish patients (n=467) | Syrian patients (n=483) | p |
|---|---|---|---|---|
| Age* | | 64 (52.75-77) | 48 (29-62) | <0.001 |
| Gender (n) | Female | 217 (46%) | 210 (43.5%) | 0.064 |
| | Male | 250 (54%) | 273 (56.5%) | |

*Median (interquartile range 25-75)

**Table 2. Analysis of age data of patients**

| Age group | Turkish patients (n=467) | Syrian patients (n=483) | Total (n=950) | p |
|---|---|---|---|---|
| <65 years | 237 (50.7%) | 383 (79.3%) | 620 (65.3%) | |
| ≥65 years | 230 (49.3%) | 100 (20.7%) | 330 (34.7%) | |
| Total | 467 (49.2%) | 483 (50.8%) | 950 (100%) | 0.000 |

**Table 3. Analysis of age data of patients**

| Age group | Turkish patients (n=467) | Syrian patients (n=483) | Total (n=950) | p |
|---|---|---|---|---|
| <20 years | 5 (1.1%) | 26 (5.4%) | 31 (3.3%) | |
| 20-29 years | 25 (5.4%) | 97 (20.1%) | 122 (12.8%) | |
| 30-39 years | 21 (4.5%) | 57 (11.8%) | 78 (8.2%) | |
| 40-49 years | 45 (9.6%) | 72 (14.9%) | 117 (12.3%) | |
| 50-59 years | 78 (16.7%) | 90 (18.6%) | 168 (17.7%) | |
| 60-69 years | 114 (24.4%) | 65 (13.5%) | 179 (18.8%) | |
| ≥70 | 179 (38.3%) | 76 (15.7%) | 255 (26.8%) | |
| Total | 467 (49.2%) | 483 (50.8%) | 950 (100%) | 0.000 |

In the under-65 age group, there was no difference in the proportions of HbA1c<6.5 and HbA1c≥6.5 (p=0.823). Among those aged 65 and older, the proportion of HbA1c<6.5 was higher in Turkish individuals, than in Syrian individuals, though this difference was not statistically significant (p=0.167). In general, the HbA1c values were similar (p=0.459) (Table 5).

The distribution of HbA1c and eGFR levels between Turkish and Syrian patients was also examined and both groups had similar distributions across HbA1c and eGFR categories There was no significant difference (p=0.710) in Table 6.

For patients with HbA1c>6.5%, the mean levels of creatinine (mg/dL), urea (mg/dL), spot urine protein/creatinine (mL/min/1.73 m²), eGFR (mL/min), AST (U/L), ALT (U/L), GGT (U/L), and ALP (U/L) showed no statistically significant differences between the groups. However, HbA1c was found to be significantly higher in the Syrian group (p<0.021) (Table 7).

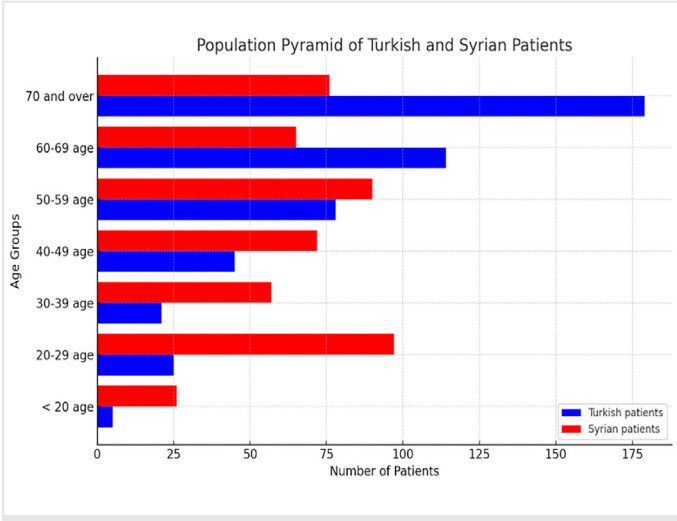



**Figure 1.** Here is the population pyramid based on the age data for Turkish and Syrian patients. The blue bars represent Turkish patients, while the red ones represent Syrian patients, broken down by different age groups

**Table 4. Analysis of age and eGFR values of patients**

| Age (years) | | eGFR ≥60 | eGFR <60 | Total | p |
|---|---|---|---|---|---|
| <65 | Turkish patients | 155 (71.4%) | 62 (28.6%) | 217 (100%) | |
| | Syrian patients | 266 (73.1%) | 98 (26.9%) | 364 (100%) | |
| | Total | 421 (72.5%) | 160 (27.5%) | 581 (100%) | 0.667 |
| ≥65 (n) | Turkish patients | 107 (50.5%) | 105 (49.5%) | 212 (100%) | |
| | Syrian patients | 38 (39.2%) | 59 (60.8%) | 97 (100%) | |
| | Total | 145 (46.9%) | 164 (53.1%) | 309 (100%) | 0.065 |

eGFR: Estimated glomerulary filtration rate

**Table 5. Analysis of patients' age and HbA1c values**

| Age group | HbA1c <6.5 (%) | HbA1c ≥6.5 (%) | Total (n) | p |
|---|---|---|---|---|
| <65 years | | | | |
| Turkish patients | 58 (56.3%) | 45 (43.7%) | 103 | |
| Syrian patients | 82 (57.7%) | 60 (42.3%) | 142 | |
| Total | 140 (57.1%) | 105 (42.9%) | 245 | 0.823 |
| ≥65 years | | | | |
| Turkish patients | 65 (63.7%) | 37 (36.3%) | 102 | |
| Syrian patients | 21 (51.2%) | 20 (48.8%) | 41 | |
| Total | 86 (60.1%) | 57 (39.9%) | 143 | 0.167 |

HbA1c: Hemoglobin A1c

**Table 6. Analysis of age, HbA1c, and eGFR values of patients**

| HbA1c Level | eGFR ≥60 (n=223) | eGFR <60 (n=157) | Total (n=380) | p |
|---|---|---|---|---|
| <6.5 | | | | |
| Turkish patients | 71 (31.80%) | 49 (22.00%) | 120 (53.80%) | |
| Syrian patients | 61 (27.40%) | 42 (18.80%) | 103 (46.20%) | |
| Total | 132 (59.20%) | 91 (40.80%) | 223 (100%) | 0.993 |
| ≥6.5 | | | | |
| Turkish patients | 44 (28.00%) | 35 (22.30%) | 79 (50.30%) | |
| Syrian patients | 47 (29.90%) | 31 (19.70%) | 78 (49.70%) | |
| Total | 91 (58.00%) | 66 (42.00%) | 157 (100%) | 0.563 |
| | | | | |
| Turkish patients | 115 (30.30%) | 84 (22.10%) | 199 (52.40%) | |
| Syrian patients | 108 (28.40%) | 73 (19.20%) | 181 (47.60%) | |
| Total | 223 (58.70%) | 157 (41.30%) | 380 (100%) | 0.710 |

HbA1c: Hemoglobin A1c, eGFR: Estimated glomerulary filtration rate

**Table 7. Biochemical analysis of patients**

| Parameter | Turkish patients (n=) | Syrian patients (n=) | |
|---|---|---|---|
| | Median (IQR) 25%-75% | Median (IQR) 25%-75% | p |
| Urea (mg/dL)* | 44.7 (29.3-85.5) | 51.0 (30.0-93.5) | 0.575 |
| Creatinine (mg/dL)* | 1.04 (0.68-1.65) | 0.81 (0.68-2.00) | 0.816 |
| eGFR (mL/dak)* | 71.0 (33.0-110.0) | 83.5 (34.0-126.0) | 0.149 |
| AST (U/L)* | 23.5 (17.5-31.5) | 21.0 (15.0-34.0) | 0.273 |
| ALT (U/L)* | 19.0 (12.0-26.0) | 15.0 (11.0-27.0) | 0.301 |
| GGT (U/L)* | 42.5 (23.5-81.0) | 32.0 (16.0-80.0) | 0.524 |
| ALP (U/L)* | 93.0 (82.9-127.5) | 100.5 (68.0-133.0) | 0.755 |
| HbA1c (%)* | 8.1 (7.2-10.3) | 9.5 (7.7-11.4) | 0.021 |
| Spot urine protein/ creatinine ratio (mg/g)* | 0.77 (0.25-1.70) | 1.10 (0.20-2.20) | 0.270 |

HbA1c: Hemoglobin A1c, eGFR: Estimated glomerulary filtration rate, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, ALT: Alanine aminotransferase, IQR: Interquartile range
*Median (interquartile range 25-75)

## Discussion

In this study, the impact of displacement due to the war in Syria on the health status of displaced individuals was investigated, with a particular focus on the development of DN, which ultimately leads to end-stage renal failure within this patient population. In this study, Syrian patients under 65 years of age were more numerous than Turkish patients. Turkish patients in the 65 and older age group were higher. A literature review revealed a study with patient ages ranging from 0 to 91, similar to our findings, and a mean age of 18.3±2.8. When patients were grouped by age (0-20, 20-40, 40-60, and over 60 years), the distribution showed 309 patients (64.5%) in the 0-20 age group, 117 patients (24.47%) in the 20-40 age group, 31 patients (6.47%) in the 40-60 age group, and 22 patients (4.59%) in the over-60 group. A study involving 251 (13). In another study conducted with 251 Syrian refugee patients, the hospitalization rate was significantly lower in patients aged 65 and above compared to those in the 19-64 age group (14). Based on this distribution, it can be concluded that children and young adults are more affected by the adverse effects of war.

Before the war, the elderly population (aged 65 and older) in Syria constituted 3.9% of the population. In Türkiye, the elderly population (65 years and older) constitutes 7.3% of the total population (15). The younger age of the patient group can be explained by the lower geriatric population density in Syria, even before the war, compared to Türkiye. The proportion of the population aged over 60 in Syria was 3.5% (16). This decrease in the proportion of the elderly population is thought to be due to the inability of the elderly to withstand the physical hardship of migration and the greater impact of external factors on them compared to younger individuals during migration.

In patients over the age of 65, the proportion of Turkish patients with eGFR >60 mL/min/1.73 m² were statistically significantly higher than that of Syrian patients. Syrian patients have undergone a difficult socio-economic life due to the war and migration, which has affected their health status and increased the risk of non-communicable diseases due to increased risk factors. With migration, there has been a deterioration in access to healthcare and living conditions. These factors may have contributed to the lower eGFR in Syrian patients. The higher prevalence of infectious diseases may also have contributed to the decrease in eGFR. In a study conducted between 2012 and 2016, 158,058 cases of diarrhea with 59 instances of bloody diarrhea, 1,299,209 cases of respiratory infections, 1354 cases of hepatitis A, and 108 active tuberculosis were reported among Syrian refugees. A total of 7,794 cases of cutaneous leishmaniasis were reported in Türkiye (17). Due to their living conditions, Syrian refugees in Türkiye can be considered a vulnerable group.

The younger age of the Syrian patient group and the higher average age of Turkish patients, who had multiple comorbidities, may have contributed to the lack of differences in creatinine, urea, spot urine protein/creatinine levels of patients with HbA1c>6.5%.

### Study Limitations

HbA1c levels can be affected by factors such as hemodialysis, pregnancy, human ımmunodeficiency virus/ acquired immunodeficiency syndrome treatment, age, ethnicity, genetic background, anemia, and

hemoglobinopathies, which should be considered when interpreting HbA1c measurements. Since our study was retrospective, the analysis was based on available data. There were some deficiencies in the history-taking process for Syrian patients due to language barriers. A study on Syrian refugee patients undergoing transplantation demonstrated that challenges in the informed consent process persist, primarily due to language barriers that restrict effective communication between healthcare providers and patients (18). A study found that effective communication was associated with healthcare providers' listening skills and willingness to understand, whereas poor communication led to misunderstandings, weakened doctor-patient relationships, and increased distrust. The study emphasized that communication challenges persisted despite the use of interpreters (19). While patients might be aware of their diagnoses, they often were unable to communicate this to the physician, and medical records were often unavailable or in Arabic. These factors contributed to a lack of knowledge about existing diagnoses. The diagnosis of DN is often made using spot urine albuminuria. However, albuminuria was not measured in our patients' lab results; instead, the protein/creatinine ratio was analyzed. The homeostatic model assessment for ınsulin resistance values of the patients could not be measured in the study due to the lack of insulin level measurements in most patients. This study is retrospective and based on the available data. Since mortality data for Syrian patients could not be determined from our hospital system, scales such as quality-adjusted life year (QALY) could not be calculated (20). One of the limitations of the study is the absence of long-term data, which complicates tracking the progression of complex health issues over time. The collection of such data would enable a more comprehensive understanding of refugee health and serve as a foundation for the development of long-term health strategies. Future research should focus on the elderly refugee population, emphasizing the importance of collecting long-term health data and ensuring continuous health monitoring for this group.

One of the limitations of this study is the potential influence of ethnic differences between the Syrian refugee and Turkish populations. Genetic predispositions, dietary habits, and cultural factors may contribute to variations in health outcomes. While this study focused on migration-related health disparities, it does not fully account for the possible effects of ethnic background on disease susceptibility and progression. Future research with a more detailed assessment of genetic and sociocultural factors is needed to better understand their role in health disparities between these populations.

## Conclusion

This study identified significant health disparities between Syrian refugees and Turkish patients, highlighting the long-term health consequences of war, forced migration, and the challenges associated with refugee status. The findings indicate that the Syrian refugee population is predominantly younger, yet elderly Syrian refugees are at a disproportionately higher risk of renal dysfunction, as evidenced by a greater prevalence in the eGFR <60 group. Additionally, significantly higher HbA1c levels among Syrian refugees suggest a heightened risk of poor glycemic control and associated complications such as DN.

The adverse health outcomes observed in the Syrian refugee population may be attributed to the combined effects of war-related trauma, disruptions in healthcare access during and after migration, and the socioeconomic hardships inherent in refugee life. Limited access to preventive care, delays in diagnosis, and inadequate management of chronic diseases further exacerbate these disparities. Therefore, targeted healthcare interventions, including early screening programs, continuous monitoring, and culturally sensitive management strategies, are essential to mitigate the long-term impact of forced migration on refugee health. Additionally, strengthening healthcare infrastructure and increasing international support for refugee health initiatives remain crucial in addressing the growing burden of chronic diseases within this vulnerable population.

### Ethics

**Ethics Committee Approval:** This study received approval from the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (approval number: 2020-227, date: 23.12.2020).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - E.Ç.Ö., H.Ö.; Concept - H.Ö., Ö.Y., N.H.Z., E.K.A.; Design - E.Ç.Ö., Ö.Y., N.H.Z., O.A., F.P.Z., Z.K.; Data Collection or Processing - E.Ç.Ö., Ö.Y., F.P.Z.; Analysis or Interpretation - E.Ç.Ö., H.Ö., O.A., Z.K.; Literature Search - E.Ç.Ö., E.K.A., F.P.Z., Z.K.; Writing - E.Ç.Ö., H.Ö.

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# Comparative Analysis of Sutured and Sutureless 25G Pars Plana Vitrectomy: Impact on Surgically Induced Astigmatism and Hypotony

Ebubekir Durmuş, Ahmad Kunbaz, Gözde Derin Şengün, Veysel Aykut, Fehim Esen, Halit Oğuz

İstanbul Medeniyet University Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

## ABSTRACT

**Introduction:** Vitreoretinal surgery has advanced with transconjunctival sutureless vitrectomy (TSV), using smaller incisions. However, TSV often causes hypotony due to sclerotomy leakage, leading to severe postoperative issues. This study compares outcomes between sutureless and sutured 25G pars plana vitrectomy (PPV) and highlights sutures' significance in TSV.

**Methods:** Fifty-four eyes underwent 25G PPV, divided into sutureless and sutured groups based on sclerotomy closure methods. Preoperative and postoperative evaluations at 1 week, 1 month, and 3 months included corrected distance visual acuity (CDVA), intraocular pressure (IOP), auto refractometer readings, and corneal topography. Special attention was given to postoperative hypotony, and surgically induced astigmatism (SIA) was assessed.

**Results:** The sutureless (mean age: 67.4±9.1 years, n=31) and sutured (mean age: 59.2±12.7 years, n=23) groups were analyzed. The sutureless group showed stable SIA at 1 and 3 months (1.39±1.1 vs. 1.30±0.9, p=0.695). The sutured group had higher SIA at 1 month (3.16±3.2 vs. 1.39±1.1, p=0.009), which decreased by 3 months (3.16±3.2 vs. 1.95±1.4, p=0.021). No significant intergroup differences were observed at the third month postoperatively. CDVA improved significantly in both groups (p<0.001), highlighting surgical efficacy. IOP was comparable to that of the sutureless group, but transient hypotony occurred in the sutureless group. IOP consistency favored the sutured group.

**Conclusion:** The study findings underscore the impact of suturing the sclerotomy ports on elevating SIA. However, it's crucial to note that SIA usually decreases by the third postoperative month, whereas hypotony-related complications can have enduring effects. Surgeons must carefully assess hypotony risks, particularly in children or in cases of high myopia, deciding on the necessity of sutures in microincisional PPV.

**Keywords:** 25-gauge pars plana vitrectomy, transconjunctival sutureless vitrectomy, surgically induced astigmatism, hypotony

## Introduction

The conventional 20-gauge (G) pars plana vitrectomy (PPV) procedure results in a significant induction of surgically induced astigmatism (SIA) during the initial postoperative phase (1). This SIA originates from changes in corneal curvature due to suturing of sclerotomy ports (2). The corneal alterations subsequent to vitrectomy have the potential to adversely affect the visual outcomes of the surgical procedure. The advancement of transconjunctival sutureless vitrectomy (TSV), facilitated by smaller incision sclerotomies, represents progress in this field. TSV has gained popularity among vitreoretinal surgeons due to its minimally invasive nature, shorter surgical duration, and elimination of the need for conjunctival dissection and scleral suturing (3,4).

TSV has also demonstrated a decreased incidence of postoperative astigmatism. However, an increased susceptibility to hypotony and endophthalmitis has been observed due to inadequate closure of sclerotomies (5,6). Poorly sealed incisions may allow ocular surface fluid and bacteria to enter the vitreous cavity. Studies have shown a higher rate of bacterial contamination within the vitreous cavity following 25G TSV compared to 20G sutured vitrectomy (7). Moreover, reports indicate that the risk of developing endophthalmitis after 25G TSV, is approximately 28 times higher than after 20G sutured vitrectomy (8). A meta-analysis has also documented elevated occurrences of hypotony and choroidal detachment in TSV compared to 20G sutured vitrectomy (9).

Currently, TSV has become the most frequently favored approach in vitreoretinal surgery. This study aims to compare the clinical outcomes

**Address for Correspondence:** Fehim Esen Assoc. Prof., MD, İstanbul Medeniyet University Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye
**E-mail:** fehimesen@yahoo.com **ORCID ID:** orcid.org/0000-0002-9518-541X

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of sutured and sutureless 25G PPV, and to elucidate the role of sutures in microincisional sutureless vitrectomy.

## Methods

This retrospective analysis included 54 eyes from 53 individuals who underwent 25G PPV at University of Health Sciences Türkiye, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Ophthalmology. All pertinent ophthalmic data were extracted from the patient records. Exclusions from the study involved patients with corneal pathologies, prior ocular surgeries except for phacoemulsification, or traumas, combined phacoemulsification and PPV procedures, systemic autoimmune disorders, and those who did not comply with follow-up appointments for a minimum of three months post-surgery. The study was approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University Göztepe Training and Research Hospital (approval no: 2022/0235, date: 13.04.2022).

The surgical approach entailed the standard 3-port 25G trocar cannula system (Alcon Laboratories, Fort Worth, Texas, USA) and was consistently performed by the same vitreoretinal surgeon, utilizing the Alcon Constellation vitrectomy system (Alcon Laboratories, Inc.). We created all sclerotomy incisions using a single-step, biplanar approach at a 30-degree oblique angle, 3.5-4 mm posterior to the limbus, depending on the phakic status, without displacing the conjunctiva. Based on the closure technique for the sclerotomy sites, patients were categorized into sutureless and sutured groups. The scleral massage method was employed for the sutureless group, while an absorbable 8/0 vicryl suture (PGA FSSB-Chirurgische Nadeln GmbH, Germany) was used for the sutured group. The sclerotomy incision site was grasped with a Colibri forceps and sutured parallel to the limbus, without conjunctival exploration. Sclerotomy closure was verified for leakage in both techniques, and the procedure was concluded only after confirming that the sclerotomies were properly closed.

Thorough ophthalmic evaluations were conducted for all patients preoperatively and at the end of the first week, first month, and third month postoperatively. These assessments encompassed auto refractometer readings (Topcon KR-1), corrected distance visual acuity (CDVA), intraocular pressure (IOP) measurements using pneumatic tonometry, slit-lamp biomicroscopy, dilated fundus examinations, and corneal topography. Patient demographics, including age, gender, etiology, and the presence of ocular and systemic diseases, were retrieved from medical records. Postoperative complications such as hypotony (IOP <8 mmHg), endophthalmitis, and vitreous hemorrhage were also documented.

Corneal topography was conducted both preoperatively and at 1 month and 3 months postoperatively using a video keratography system (Tomograph and Corneal Topographer, Sirius, Scandicci, Italy). Three consecutive topographic images were acquired per eye at each measurement point, with the best-aligned and fixed image selected for analysis. Data on anterior corneal astigmatism, mean keratometry (Km), flat (K1), and steep (K2) keratometry readings within the central 3 mm of the corneal front surface were recorded. SIA denotes the degree and axis of astigmatic change caused by the surgery. We preferred Alpins' method for the calculation of SIA using vector analysis (10). Vector analysis was performed by the automated software (11).

### Statistical Analysis

Data analysis was performed using SPSS 17 software (SPSS for Windows, SPSS, Inc., Chicago, IL, USA). The normality of the data distribution was assessed via the Kolmogorov-Smirnov test and visualized through histograms and probability graphs. Descriptive statistics encompassed mean ± standard deviation for normally distributed data and median with interquartile range for non-normally distributed data. The Mann-Whitney U-test facilitated intergroup comparisons, while Wilcoxon tests (for non-normally distributed data) gauged differences between preoperative and postoperative measurements. The Friedman test was used for comparisons among three or more matched groups, and the chi-square test evaluated categorical data.

## Results

The study comprised thirty-one patients in the sutureless group (19 male, 12 female, mean age: 67.4±9.1 years) and twenty-three patients in the sutured group (14 male, 9 female, mean age: 59.2±12.7 years). In the sutureless group, the most prevalent indication for surgery

**Table 1. Demographic and clinical characteristics of the patients**

| | Sutureless group | Sutured group | p-value |
|---|---|---|---|
| Mean age (years ± SD) | 67.4±9.1 | 59.2±12.7 | 0.040* |
| Sex (M/F) | 19/12 | 14/9 | 0.975** |
| Eye laterality (R/L) | 14/17 | 12/11 | 0.610** |
| Diabetes mellitus (n) | 16 | 9 | 0.363** |
| Hypertension (n) | 16 | 10 | 0.554** |
| **Etiology** | | | |
| Epiretinal membrane | 7 | 3 | |
| Vitreous hemorrhage | 14 | 5 | |
| Retinal detachment | 4 | 10 | |
| Macular hole | 5 | 3 | |
| Vitreomacular traction | 1 | 1 | |
| Dropped intraocular lens | | 1 | |
| Surgical time (minutes ± SD) | 47.3±18.6 | 75.1±36.9 | 0.004* |
| **Tamponde usage** | | | 0.003** |
| Air | 14 | 5 | |
| Sulfur hexafluoride (SF6 20%) | 7 | 3 | |
| Octafluoropropane (C3F8 14%) | 9 | 5 | |
| Silicon oil | 1 | 10 | |

*Mann-Whitney U-test, **Pearson chi-square test
SD: Standard deviation, M: Male, F: Famale, R: Right, L: Left

was diabetic vitreous hemorrhage, while in the sutured group, it was retinal detachment. Comprehensive details regarding the patients' demographic and clinical data can be found in Table 1.

Comparisons of K1, K2, and astigmatism values between preoperative and postoperative measurements at the first and third months revealed similarity in the sutureless group (p>0.05). In the sutured group, a noteworthy increase was observed in the mean K2 values (43.3±1.9 vs. 44.8±2.8, p=0.003) and corneal astigmatism (-1.2±0.8 vs. -2.6±2.9, p=0.012) at the 1-month mark compared to preoperative values. However, this disparity diminished and became statistically insignificant at the 3-month postoperative point (p=0.584, p=0.976, respectively) (Table 2). SIA was notably greater in the sutured group than the sutureless group at 1 month postoperatively (3.16±3.2 vs. 1.39±1.1, p=0.009). The SIA was reduced in the sutured group after 3 months (3.16±3.2 vs. 1.95±1.4, p=0.021), and no statistically significant distinction was observed between the groups at the third postoperative month (1.30±0.9 vs. 1.95±1.4, p=0.122, respectively) (Figure 1). Within the sutureless group, there was a slight indication of decreased SIA at 3 months postoperatively (1.39±1.1 vs. 1.30±0.9, p=0.695).

CDVA demonstrated a significant improvement in both groups over the follow-up periods. Preoperative and postoperative measurements taken at week 1, month 1, and month 3 mean logMAR CDVA measurements in the sutureless and sutured groups were 1.71±1.1 vs. 2.10±1.0, p=0.160; 1.62±1.2 vs. 1.83±1.0, p=0.178; 1.03±0.9 vs. 1.52±1.0, p=0.022; and 0.92±0.9 vs. 1.20±1.0, p=0.260, respectively. While IOP on postoperative day 1 was similar between the sutureless and sutured groups (18.9±6 vs. 17.8±4, p=0.617, respectively), the range of IOP distribution was wider in the sutureless group (Figure 2). Two patients in the sutureless group experienced hypotony (IOP <8 mmHg) on postoperative day 1, which resolved in subsequent follow-up visits. Preoperative and postoperative week 1, month 1, and month 3, IOP distribution in the sutureless and sutured groups was 19.2±7 vs. 17.3±6, p=0.280; 14.6±3 vs. 15.7±3, p=0.334; 16.7±5 vs. 16.3±4, p=0.867; and 17.4±6 vs. 15.8±4, p=0.356, respectively. The IOP trends across follow-up visits are illustrated in the graph in Supplementary Figure 1. Notably, severe complications such as suprachoroidal hemorrhage and endophthalmitis were absent in both groups. Postoperative vitreous hemorrhage occurred in one patient in the sutureless group and four patients in the sutured group. All instances of vitreous hemorrhage were attributed to recurrent hemorrhages stemming from diabetic retinopathy, and they resolved spontaneously without any intervention.

## Discussion

Fuji et al. (12) introduced the concept of 25G vitrectomy as a TSV in 2002. Subsequently, in 2005, Eckardt (13) described 23G PPV. TSV emerged with advantages such as reduced surgical time, diminished suture-associated inflammation, and SIA, along with accelerated healing of sclerotomy

**Table 2. Corneal topography changes during follow-up periods**

| | Parameters | Preoperative | 1st month (30th day) | p value | 3rd month (90th day) | p-value |
|---|---|---|---|---|---|---|
| Sutureless group | K 1, front (D) | 43.1±2.2 | 42.9±2.2 | 0.434* | 43.0±1.9 | 0.670* |
| | K 2, front (D) | 43.8±2.2 | 43.8±2.2 | 0.882* | 43.9±2.1 | 0.281* |
| | Astig, front (D) | -1.11±1.0 | -0.61±1.1 | 0.244** | -1.02±0.7 | 0.471** |
| Sutured group | K 1, front (D) | 42.4±1.9 | 42.2±1.8 | 0.390* | 42.2±1.9 | 0.491* |
| | K 2, front (D) | 43.3±1.9 | 44.8±2.8 | **0.003*** | 43.5±1.9 | 0.584* |
| | Astig, front (D) | -1.2±0.8 | -2.6±2.9 | **0.012**** | -1.4±1.1 | 0.976** |

K1: Flat axis keratometry, K2: Steep axis keratometry, Astig: Astigmatism, D: Diopter, *Paired-sample t-test, ** Wilcoxon test; Each p value shows the statistical difference from the preoperative values

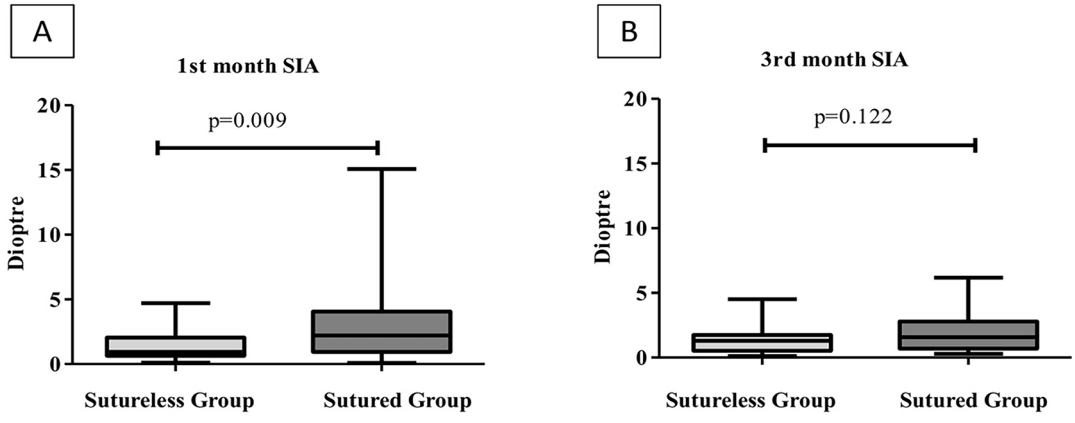



**Figure 1.** (A,B) Surgically induced astigmatism at the first and third months postoperatively in sutureless and sutured groups. Surgically induced astigmatism (SIA) exhibited a higher magnitude in the sutured group during the first month following the surgical procedure (**Figure 1A**). Subsequently, SIA reduced significantly, and by the third month postoperatively, no statistically significant disparity was observed between the sutureless and sutured groups (**Figure 1B**)

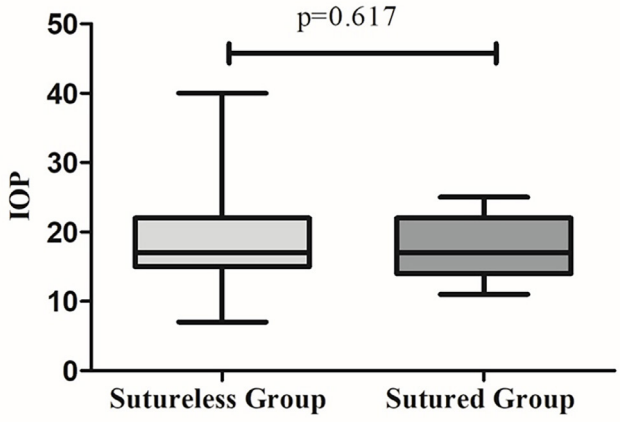



**Figure 2.** Intraocular pressure distribution on the first postoperative day in sutureless and sutured groups. No statistically significant discrepancy in intraocular pressure (IOP) was detected between the two groups on the first postoperative day. However, it is noteworthy that the sutureless group displayed a wider range of IOP variation on the first postoperative day, while IOP values in the sutured group demonstrated greater consistency

wounds (14). However, hypotony has emerged as a common complication following TSV, primarily due to leakage from the sclerotomy sites, which can lead to serious postoperative issues, including endophthalmitis and suprachoroidal hemorrhage (15). In 2010, a novel 27G microincisional sutureless vitrectomy system was introduced; however, its primary application was predominantly restricted to macular surgeries (16,17). The present study aimed to investigate the role of sutures in TSV and to perform a comparative analysis of clinical outcomes between sutured and sutureless 25G vitrectomy.

The study revealed that sutureless 25G PPV did not lead to a noteworthy alteration in corneal astigmatism during both the early and later postoperative periods. However, a notable increase in SIA was observed after sutured, 25G PPV. This aligns with previous reports, that indicated 25G TSV did not induce significant SIA, even in the early postoperative stage (18). A comparison between 23G and 25G TSV and conventional 20G PPV demonstrated that while 23G and 25G TSV had minimal impact on corneal topography, significant changes were noted following 20G vitrectomy. These changes returned to preoperative levels by the third month postoperatively (19). The origin of SIA in PPV has often been attributed to scleral cauterization and suturing of the sclerotomy sites (20). The findings of the current study corroborate these hypotheses. Similar to the conventional 20G PPV data, the application of scleral sutures, induced significant corneal astigmatism even in the context of 25G PPV with smaller incisions. Importantly, these corneal curvature changes resolved by the third postoperative month.

Hypotony, a notable concern post-TSV, is predominantly attributed to sclerotomy leakage (21). Hypotony, in turn, escalates the risk of endophthalmitis by facilitating the ingress of ocular surface microorganisms into the vitreous cavity (22). Additionally, hypotony can trigger maculopathy, choroidal detachment, and choroidal hemorrhage (22,23). Acar et al. (15) reported hypotony rates of 26.12%, 17.11%, and 8.10% at 2 hours, 1 day, and 1 week respectively, following 25G TSV. Schweitzer et al. (24) highlighted hypotony as the most frequent complication (21.1%) on the first postoperative day after 23G TSV, noting its resolution within subsequent days. Reported rates of postoperative hypotony range from 0% to 5.3% in 27G TSV cases in adults, and 0% to 40% in children after 25G TSV, according to the study by WenTao et al. (25) Additionally, they found a 10.5% incidence of hypotony in pediatric patients undergoing 27G TSV. Given the higher susceptibility of pediatric eyes to postoperative hypotony, routine suture placement may be considered to enhance wound closure and maintain stable IOP in these pediatric cases. In our study, two patients in the sutureless group experienced transient hypotony on the first postoperative day, with recovery within a week. Notably, no complications associated with hypotony were observed, and IOP values showed greater consistency in the sutured group.

The risk of endophthalmitis has been reported to be higher in TSV compared to sutured 20G PPV (26). Factors such as reduced infusion flow, retained peripheral vitreous, insufficient scleral wound closure, early postoperative hypotony, and wound distortion due to eye rubbing contribute to the elevated risk of endophthalmitis following TSV (27-29). In a substantial case series, Kunimoto and Kaiser (30) reported endophthalmitis incidence of 0.018% in 20G PPV and 0.23% in 25G TSV, indicating a 12-fold higher risk with TSV. However, Oshima et al. (31) found no significant disparity in endophthalmitis incidence between 23G and 25G TSV and 20G PPV, attributing this favorable trend to stringent antiseptic protocols and suturing of sclerotomies. Shimada et al. (32) similarly reported a comparable incidence of endophthalmitis (0.03%) for 25G TSV and 20G PPV, noting peripheral vitreous removal, suturing of sclerotomy sites in cases of inadequate closure, and conjunctival irrigation as contributing factors to their differing results.

Visual acuity gradually improved over follow-up in both groups. In the sutured group, SIA decreased by the third postoperative month, resulting in the highest CDVA at that point. Nonetheless, no statistically significant difference was observed between the groups by the third postoperative month.

### Study Limitations

It's important to note that this study is the first to compare the clinical outcomes of sutured and sutureless 25G PPV. However, it does carry limitations such as its retrospective design, relatively small sample size, variations in the tamponade use between the groups, and relatively short follow-up duration. Additionally, due to the rarity of certain complications, particularly endophthalmitis and choroidal detachment, the study was limited in comparing these aspects between the groups.

## Conclusion

The study highlights that sutureless 25G PPV is linked to minimal changes in corneal astigmatism during both the early and late postoperative phases, in contrast to sutured 25G PPV, which demonstrated a notable increase in SIA. The study reaffirms the significance of sutures in impacting PPV-induced astigmatism, outweighing the influence of incision size. It's crucial to note that the SIA induced by sutures in 25G PPV is transient and that the effects resolve by the third postoperative month, whereas complications related to hypotony may have more enduring effects. Hence, surgeons should carefully evaluate individual risks and make

informed decisions regarding suture placement, especially in high-risk cases such as pediatric patients or those with high myopia.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University Göztepe Training and Research Hospital (approval no: 2022/0235, date: 13.04.2022).

**Informed Consent:** Retrospective study.

### Footnotes

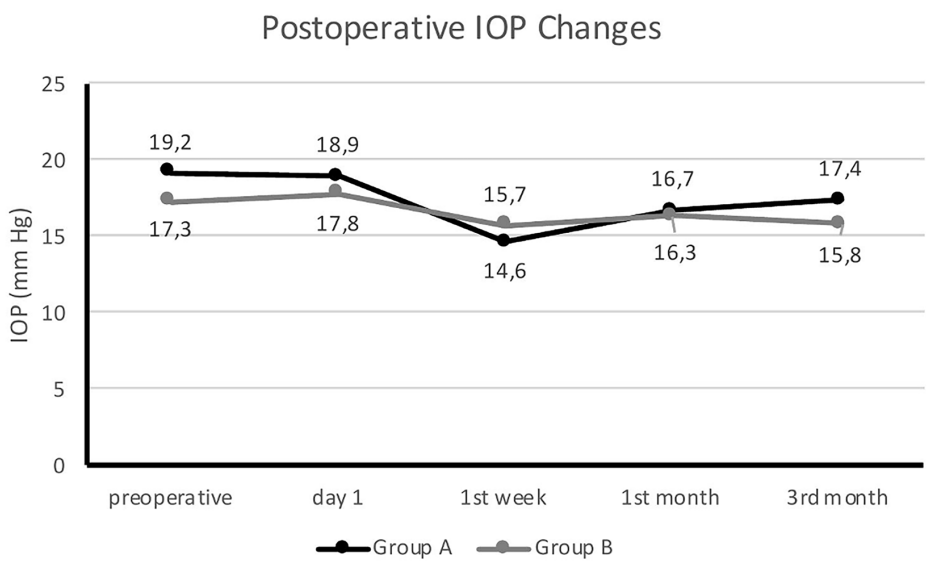
**Authorship Contributions:** Surgical and Medical Practices - E.D., V.A.; Concept - E.D., V.A., H.O.; Design - E.D., V.A., H.O.; Data Collection or Processing - E.D., A.K., G.D.Ş.; Analysis or Interpretation – E.D., F.E.; Literature Search - A.K., G.D.Ş.; Writing – E.D., A.K., F.E.

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**Supplementary Figure 1.** Intraocular pressure (IOP) trends in the sutureless and sutured groups.
No statistically significant differences were observed between the groups at the follow-up visit ($p>0.05$)

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# Estimation of Alexithymia by Body Fat Ratio in Adolescents with Overweight and Obesity

Nazan Kaymaz[1], Hande Şirin[2], Mehmet Erdem Uzun[2], Özlem Kara[3]

[1]İstinye University Liv Hospital, Department of Pediatrics, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Child and Adolescent Psychiatry, Bursa, Türkiye
[3]University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital, Clinic of Child Endocrinology, Bursa, Türkiye

## ABSTRACT

**Introduction:** This study investigated the association between adiposity and alexithymia risk among adolescents with overweight (OW) and obesity (OB).

**Methods:** In this cross-sectional study, adolescents who are OW or obese completed a sociodemographic questionnaire and the Toronto Alexithymia Scale (TAS). Anthropometric measurements-including weight, height, waist, and hip circumference-were collected, and body fat percentage was determined via bioelectrical impedance analysis. Participants were categorized into two groups based on the presence or absence of alexithymia, and statistical comparisons were conducted using appropriate parametric and non-parametric tests. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive value of adiposity indices.

**Results:** The study included 105 adolescents (69 females, 36 males). Alexithymia was present in 49.5% of participants, with a significantly higher prevalence among females (77%). Total TAS scores were positively correlated with body fat percentage and waist-to-height ratio (WHtR). A body fat percentage above 35.5% and WHtR over 0.61 showed moderate diagnostic performance, with respective sensitivities of 71.15% and 75%, and specificities of 54.72% and 65.51%. The area under the ROC curve was 0.632 [95% confidence interval (CI): 0.533-0.724] for body fat and 0.622 (95% CI: 0.522-0.715) for WHtR.

**Conclusion:** Among adolescents with OW or OB, those with a body fat percentage over 35.5% or a WHtR above 0.61-particularly females-may have an increased risk of alexithymia. These findings underscore the need for integrating emotional and metabolic assessments in the clinical care of this population.

**Keywords:** Adolescents, obesity, body fat mass, alexithymia

## Introduction

The excessive accumulation of body fat is linked to an increased risk of cardiometabolic diseases as well as a higher likelihood of developing psychiatric issues. Studies show that individuals with overweight (OW) and obesity (OB) have a higher incidence of mental disorders, including reduced cognitive function, impaired mental and intellectual function, anxiety, and depression (1). Structural and functional brain changes in individuals with these disorders have been identified through neuroimaging studies (2). The commonly used tool for diagnosing and monitoring OB and predicting related health complications is the body mass index (BMI). However, using BMI as an indicator of OB is flawed due to its inability to consider variations in body composition or the distribution of body fat. In recent years, it has been shown that anthropometric measurements like waist circumference (WC), waist-to-height ratio (WHtR), and waist-to-hip ratio (WHR) are more effective than BMI in predicting metabolic and cardiovascular complications associated with OB (3). Furthermore, it has been proven through various studies that the distribution and amount of body fat are the primary factors that link OB to complications. Moreover, this phenomenon has led to a new definition of "normal weight OB," which refers to cases with normal BMI and body fat ratio above 30 percent (4).

Alexithymia is a psychiatric disorder with an increasing prevalence among individuals with OB (5). The term "alexithymia" originates from Greek and signifies the inability to express emotions verbally. It is defined by a limited imagination, a lack of emotional expression, and a cognitive approach that emphasizes the outer environment.The etiological factors include genetic, physiological, and psychosocial influences. Additionally, neurochemical and neuroanatomical elements play a role (6).

**Address for Correspondence:** Nazan Kaymaz Prof., MD, İstinye University Liv Hospital, Department of Pediatrics, İstanbul, Türkiye
**E-mail:** drnazan_erdal@hotmail.com **ORCID ID:** orcid.org/0000-0002-3962-4799

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The correlation between alexithymia as a psychological construct and OB has been investigated for over two decades. In individuals with OB, alexithymic behavior is likely to manifest more frequently as a coping strategy for stressors (7).

On the other hand, it is essential to note that alexithymia may contribute to OB (5). Negative emotions experienced by alexithymic individuals can increase overeating as a somatic response (8). Adolescents exhibiting alexithymia tend to engage in more episodes of uncontrolled eating and eating when not hungry. Difficulties in expressing emotions, especially during stressful times, can increase overeating episodes (9). Cognitive deficits in distinguishing bodily sensations (such as hunger or fullness) from emotions may explain this relationship. Alexithymia not only predisposes individuals to weight gain but also maintains OB and predicts treatment inefficiency and termination (10). These data emphasize the importance of identifying the link between OB and alexithymia due to their causal ambiguity. Although many studies indicate a higher occurrence of alexithymia in individuals with OB, no research has explored its correlation with body fat mass (BFM). This study aimed to determine whether alexithymia in adolescents with OW and OB is related to BFM.

## Methods

### Participants and Study Design

This is a cross-sectional study of adolescents followed for the diagnosis of exogenous OB and OW at University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital's pediatric endocrinology clinic. Exogenous OB was defined as OB that is not connected to any genetic causes and it is not associated with endocrine or metabolic conditions. Participants with conditions other than OB or its related comorbidities, as well as those with mental or neurological disorders and eating disorders, were excluded from the study. The study was reviewed by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2023/02-14, date: 22.02.2023) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Both verbal and written informed consent was collected from all participants and their parents.

### Sociodemographic Data Collection

Information was collected through a questionnaire that included age, gender, birth week, delivery mode, birth weight, school success, parents' ages and education levels, and family income. The school success of the adolescents was assessed based on their self-description and categorized into three levels: low, medium, or high. Families self-reported their economic status and categorized it as low, medium, or high. Parents' educational levels were categorized as follows: uneducated (cannot read or write), elementary school, middle school, high school, and university.

### Anthropometric Measurements

The measurements were performed between 8:00 and 9:00 a.m. after an overnight fast of at least 8 hours and with an empty bladder.

### Body Weight, Body Height, and Body Mass Index

Body weight and height were measured in underwear and no shoes. A stadiometer, which was calibrated daily, was employed to determine the height of all patients, while body weight was measured using a scale (Seca 703, with an accuracy of 100 g, SecaGmBH&Co Kg, Hamburg, Germany). Height was measured with a precision of 0.1 cm. Weight was recorded with an accuracy of 0.1 kg. The BMI was calculated using the formula: weight (kg)/height $(m)^2$. Additionally, the BMI z-score was determined using the World Health Organization reference with the AnthroPlus calculator [version 1.0.4, World Health Organization (WHO)] (11). A BMI between the $85^{th}$ and $95^{th}$ percentile was categorized as OW, a BMI above the $95^{th}$ percentile was classified as having OB, with a BMI of 35 or greater defined as severe OB (12).

### Waist and Hip Circumferences

(WC, in cm) and hip circumference (HC, in cm) were assessed with an inelastic tape, which has an accuracy of 0.1 cm. The WC was taken at the midpoint between the lower rib and the top of the iliac crest during expiration, while the HC was taken at the maximum protuberance of the buttocks. An average of two measurements for each parameter was recorded. The WHR was computed as WC divided by HC, and the WHtR was determined by dividing WC by the measured height in centimeters.

### Measurement of Body Fat Mass

BFM was assessed using a bioelectrical impedance analysis (BIA) method with a TANITA BC418-MA electronic scale. TANITA BC 418-MA is an electrode system with 8 contact points, that can evaluate body composition segmentally without the use of gel electrodes. To assess fluid balance, females were evaluated between 6 and 10 days after their menstrual cycle. The subjects verbally confirmed their adherence to these criteria before participating. Subject details, including gender, height, and age, were entered manually, and a standard adjustment of 0.5 kg for the weight of clothing was applied to all participants.

### The Assessment of Alexithymia

The Turkish version of the 3-factor structure of the Toronto Alexithymia Scale (TAS-20) was used to assess alexithymia. The scale, which is based on Likert-type self-reporting, contains 20 sentences and includes 3 subfactors (difficulty identifying emotions, difficulty describing emotions, and externally oriented thinking). The Cronbach's alpha value of the scale is 0.85 for all items; $\alpha$dif =0.83 and $\alpha$ddf =0.75 for the 3 subscales indicate good internal consistency of these subscales. Meanwhile, $\alpha$eot =0.60 indicates borderline consistency. The lowest score is 20, the highest score is 100, and higher scores indicate greater impairment/difficulty. The cut-off values of the scores are determined

as follows: alexithymia (score ≥61), possible alexithymia (score between 52 and 60), and absence of alexithymia (score ≤51) (13). Two groups were created for statistical comparison: participants were divided into those with alexithymia and those without alexithymia based on a cut-off value of 61. Consequently, borderline patients were analyzed in the non-alexithymia group. Since the participants in the study filled out the data completely, no additional editing was required in terms of missing data.

### Variables in the Laboratory

The participants' most recent laboratory values recorded in the hospital system were used, including alanine transaminase, fasting plasma glucose, fasting serum insulin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and total cholesterol. The insulin resistance index was calculated using the homeostatic model assessment-insulin resistance (HOMA-IR) formula: (fasting plasma glucose × fasting serum insulin)/22.5.

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM, Chicago, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Mean differences between two independent groups (alexithymia vs. non-alexithymia) were evaluated using the Student's t-test for normally distributed variables and the Mann-Whitney U test when parametric assumptions were not met. The chi-square test was used to compare categorical variables. Correlation analyses were conducted using the Pearson correlation coefficient (r), with an r-value above 0.300 considered meaningful regardless of statistical significance. Receiver operating characteristic (ROC) analysis was performed using MedCalc version 16.8 (MedCalc Software, Ostend, Belgium) to assess the diagnostic performance of body composition parameters in predicting alexithymia. A two-tailed p-value of <0.05 was considered statistically significant.

## Results

We analyzed data from 105 adolescents, consisting of 69 girls and 36 boys, with a mean age of 14.84 years and a BMI of 32.24±5.17. The study found that 52 people, who is 49.5% of the population, had alexithymia based on TAS scores. Participants were divided into two groups: those with and without alexithymia. There was no significant difference in the pubertal stage between the groups (p=0.87). The alexithymia group had a higher proportion of females (77%, p=0.01). Table 1 compares the demographic characteristics of subjects with alexithymia and those without.

**Table 1. Comparison of demographics of adolescents with OW and OB between those with and without alexithymia**

| | | Subjects with alexithymia n=52 | Subjects without alexithymia n=53 | p |
|---|---|---|---|---|
| **Age (years)** | | 14.57±1.84 | 15.11±1.80 | 0.12# |
| **Gender*** | | | | |
| Male | | 12 (23) | 24 (45) | **0.01α** |
| Female | | 40 (77) | 29 (55) | |
| **Birth weight (gr)** | | 3.330±668.30 | 3.210±624.35 | 0.407# |
| **Delivery mode*** | NVD | 29 (56) | 21 (40) | |
| | C/S | 23 (44) | 32 (60) | 0.070α |
| **Birth week*** | <37th GW | 9 (17) | 12 (23) | |
| | ≥37th GW | 43 (83) | 41 (77) | 0.330α |
| **Mother's age (year)** | | 41.56±4.88 | 41.83±5.21 | 0.783¶ |
| **Mother's education*** | Uneducated | 2 (4) | 4 (7) | |
| | Elementary school | 25 (48) | 23 (43) | |
| | Secondary school | 14 (27) | 12 (23) | |
| | High school | 6 (11) | 6 (11) | 0.830α |
| | University | 5 (10) | 6 (16) | |
| **Father's age (year)** | | 44.10±4.91 | 46.04±4.99 | 0.058# |
| **Father's education*** | Uneducated | 2 (4) | 2 (4) | |
| | Elementary school | 19 (37) | 22 (41) | |
| | Secondary school | 14 (27) | 13 (25) | |
| | High school | 8 (15) | 9 (17) | 0.546α |
| | University | 9 (17) | 7 (13) | |
| **Socio-economic status*** | Low | 1 (2) | 1 (2) | |
| | Medium | 34 (65) | 38 (72) | 0.778α |
| | Good | 17 (33) | 14 (26) | |
| **School success*** | Low | 1 (2) | 1 (2) | |
| | Medium | 28 (54) | 28 (53) | 0.994α |
| | Good | 23 (44) | 24 (45) | |

OW: Overweight, OB: Obesity, GW: Gestational week, NVD: Normal vaginal delivery, C/S: Cesarean section. Values are reported as mean ± standard deviation. *n (%), #Mann-Whitney U test, ¶Student's t-test, αChi-square test

### Anthropometric Measurements

Anthropometric measurements did not significantly differ between participants with and without alexithymia, except for their WHtR (Table 2, part 1).

### Body Composition by BIA

The groups had similar total BFT (p=0.13) and trunk fat mass (kg) (p=0.10), but significantly different percentages of body fat and trunk fat (p=0.01 and p=0.02, respectively) (Table 2, part 2).

### Comparison of Laboratory Values Between the Groups

There was no significant statistical difference in the laboratory measurements across the groups (Table 3).

More than half of the 52 participants with alexithymia were found to have severe OB. However, no correlation was discovered between the severity of OB and TAS scores (67.61±5.67) (p=0.29).

**Table 2. Comparison of anthropometrics and BIA results between OW and OB subjects with and without alexithymia**

| | Subjects with alexithymia n=52 | Subjects without alexithymia n=53 | Between-group difference (95% CI), p-value/$\chi^2$, p-value |
|---|---|---|---|
| **Part 1, anthropometrics** | | | |
| Weight, kg | 87.40±19.52 | 87.99±17.16 | 0.78# |
| Height, cm | 163.95±7.71 | 165.47±8.13 | 0.32¶ |
| BMI, kg/m$^2$ | 35.52±5.48 | 31.96±4.88 | 0.58¶ |
| BMI z-score | 2.72±0.74 | 2.58±0.80 | 0.34¶ |
| Waist circumference, cm | 106.55±14.02 | 103.23±14.60 | 0.20# |
| WHtR | 0.65±0.07 | 0.62±0.08 | **0.04¶** |
| Hip circumference, cm | 116.32±11.12 | 115.36±10.27 | 0.64¶ |
| WHR | 0.91±0.07 | 0.89±0.08 | 0.15¶ |
| **Part 2, body composition by BIA** | | | |
| Trunk fat mass, kg | 15.13±5.17 | 13.54±4.53 | 0.10# |
| Trunk fat mass, % | 33.80±7.21 | 30.48±7.49 | **0.02¶** |
| Total body fat, kg | 34.97±12.64 | 31.40±11.16 | 0.13# |
| Total body fat, % | 39.08±7.51 | 35.31±7.63 | **0.01¶** |
| **Part 3, TAS-20 measures, mean (SD)** | | | |
| Subscale 1 | 24.75±4.13<br>24 (22-28) | 14.89±4.46<br>15 (12-18.5) | **<0.001¶** |
| Subscale 2 | 16.81±2.53<br>16 (15-18.75) | 12.11±2.93<br>12 (10.5-14.5) | **<0.001#** |
| Subscale 3 | 25.96±3.38<br>26 (24.2-28) | 23.02±4.19<br>22 (21-26) | **<0.001#** |
| Total score | 67.52±5.46<br>63 (60-70.75) | 50.04±8.31<br>51 (47-57) | **<0.001#** |

OW: Overweight, OB: Obesity, SD: Standard deviation, BMI: Body mass index, WHtR: Waist-height ratio, WHR: Waist-to-hip ratio, BIA: Bioelectrical impedance analysis, CI: Confidence Interval, TAS-20: Toronto Alexithymia Scale, Subscale 1: Difficulty identifying feelings, Subscale 2: Difficulty describing feelings, Subscale 3: External-oriented thinking.
Values are reported as mean ± SD or median (25$^{th}$ and 75$^{th}$ percentiles). Significant contrasts are marked in bold.
#Mann-Whitney U test, ¶Student's t-test, "Chi-square test

**Table 3. Comparison of laboratory results between the groups**

| Values | Subjects with alexithymia n=52 | Subjects without alexithymia n=53 | p# |
|---|---|---|---|
| ALT (U/L) | 24.77±19.43 | 21.53±11.20 | 0.90 |
| HDL-C (mg/dL) | 47.76±11.13 | 48.92±11.16 | 0.69 |
| LDL-C (mg/dL) | 89.57±26.95 | 93.51±27.66 | 0.24 |
| TG (mg/dL) | 99.65±48.69 | 102.83±44.650 | 0.47 |
| TC (mg/dL) | 156.02±38.59 | 162.92±31.44 | 0.31 |
| HOMA-IR | 4.66±2.69 | 4.04±2.42 | 0.28 |

Values are reported as mean ± standard deviation, #Mann-Whitney U test.
ALT: Alanine transaminase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, TC: Total cholesterol, HOMA-IR: Homeostatic model assessment for insulin resistance

The number of participants with OW, OB, and severe OB among female participants was 5, 11, and 24, respectively. Among male participants, the count was 4, for each category. In the OB classification, with a mean age of 15.08±1.70, the severe OB group was found to be statistically significantly older (p=0.03). It is worth noting that a significant majority of female participants fell into the severe OB category, constituting 62% of them (p=0.01).

Table 4 presents the comparison of anthropometric and body fat measurements in the alexithymic group. No significant difference between genders was noted.

The correlation analysis revealed a positive correlation between total alexithymia score and body fat percentage and waist-height ratio.

The correlation coefficients were 0.21 (p=0.03) and 0.24 (p=0.01), respectively, as depicted in Figures 1a, b.

A ROC analysis was carried out on the participants to identify the total body fat (%) cut-off value that could potentially predict the presence of alexithymia. The Area Under the Curve (AUC) has been calculated to be 0.632 with a 95% confidence interval (CI) of 0.533-0.724. The sensitivity and specificity diagnostic accuracies are 71.15% and 54.72%, respectively (Figure 2a).

A second ROC analysis was performed to assess the impact of the WHtR. It has been determined that a WHtR of greater than 0.61 is the cut-off value for identifying alexithymia. The AUC was 0.622 (with a 95% CI of 0.522-0.715), and the diagnostic accuracy was 75%. The sensitivity and specificity were both 65.51% and the results are shown in Figure 2b.

**Table 4. Anthropometric measurements and body fat values of the alexithymic group by gender**

| | Females (n=40) | Males (n=12) | p |
|---|---|---|---|
| Trunk fat mass, kg | 15.32±5.10 | 14.49±5.58 | 0.52# |
| Trunk fat mass, % | 24.05±7.26 | 33.13±7.13 | 0.70¶ |
| Total body fat, kg | 34.89±12.22 | 35.25±14.52 | 0.99# |
| Total body fat, % | 38.99±6.27 | 39.40±11.31 | 0.24# |
| Waist circumference, cm | 91.33±7.51 | 103.13±12.58 | 0.74¶ |
| WHtR | 0.65±0.07 | 0.65±0.06 | 0.84¶ |
| Hip circumference, cm | 116.08±10.09 | 117.12±14.56 | 0.78¶ |
| WHR | 0.91±0.08 | 0.92±0.03 | 0.80¶ |

Values are reported as mean ± SD, SD: Standard deviation, WHtR: Waist-height ratio, WHR: Waist-to-hip ratio. #Mann-Whitney U test, ¶Student's t-test

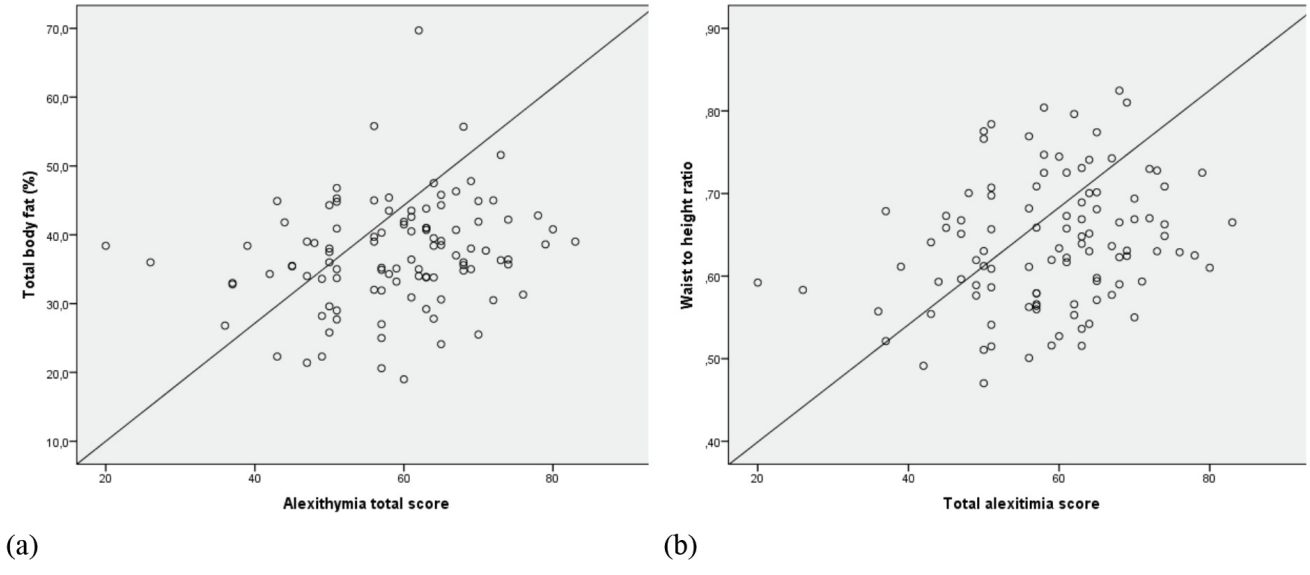



**Figure 1.** (a) the correlation between study population's total body fat (%) and TAS (b) the correlation between study population's waist-to-height ratio and TAS

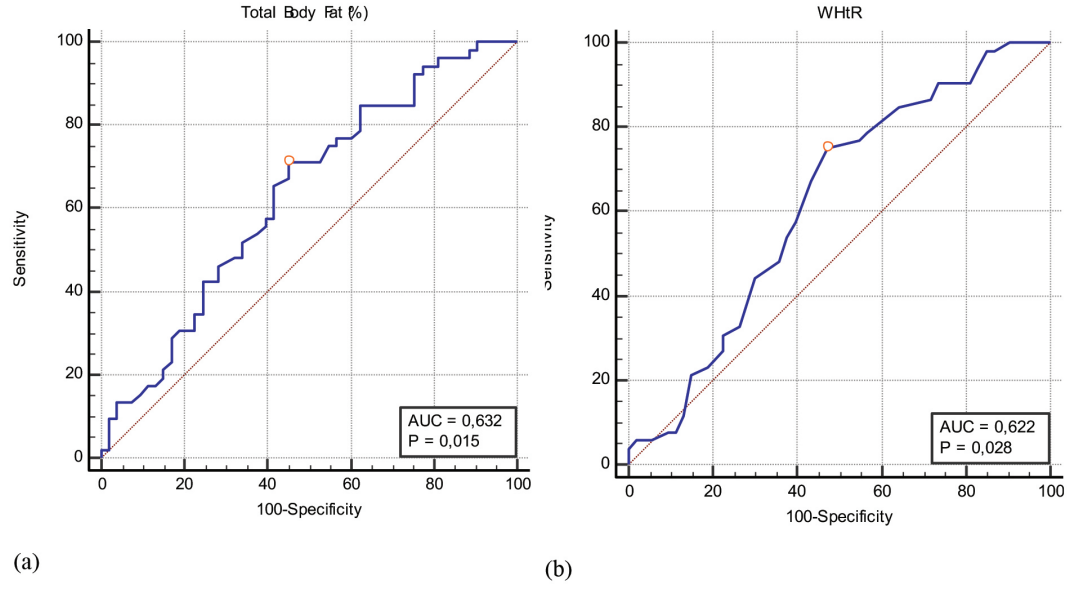



**Figure 2.** Receiver operating characteristic (ROC) curve of the predictive model of (a) total body fat percentage based on TAS scores (b) waist-to-height ratio based on TAS scores
TAS: Toronto Alexithymia Scale

## Discussion

The findings revealed that having a BFT of more than 35.5% could suggest the existence of alexithymia. Notably, 45.2% of adolescents with OW or OB in the present study exhibited alexithymia, a rate higher than previously reported in similar populations (14). Initially, we considered that this might stem from a greater proportion of participants being obese or severely obese, unlike earlier studies where most were OW (15). However, alexithymia scores did not demonstrate a progressive increase across OB severity categories. This indicates that among adolescents whose BMI exceeds 25, the presence of alexithymia is more closely associated with body fat percentage than with BMI alone.

These results support growing concerns that BMI is insufficient as a standalone indicator of OB-related complications. Given that BMI values in children and adolescents vary by age and sex, BMI percentile values are used for classification (16). International references include the WHO (2007) and IOTF (2000; updated 2012) growth standards (17,18). However, several studies have highlighted limitations in OB classification based solely on BMI, leading to the adoption of complementary measures such as WC, WHR, and WHtR (19-21). Among these, WHtR has been shown to be a less age-dependent reliable indicator of central adiposity and metabolic risk.

In our study, both body fat percentage and trunk fat percentage were significantly higher in adolescents with alexithymia, while WHtR emerged as a more effective anthropometric predictor than other indices.

Prior studies have linked elevated visceral fat to psychiatric symptoms such as anxiety and depression (22,23), possibly via increased cytokine production (24) and chronic activation of the hypothalamic-pituitary-adrenal axis (25). Some literature suggests a potential association between visceral fat and alexithymia, though the relationship remains complex and causality is yet to be clearly established (26). Alexithymia may, in turn, exacerbate OB-related mental health vulnerabilities by impairing body perception and emotion regulation (5,10).

Incorporating WHtR into clinical screening for alexithymia in OW/obese adolescents may offer practical benefits, particularly in endocrinology clinics where psychiatric assessments are not routinely conducted. Identifying alexithymia through anthropometric indicators could facilitate earlier psychological referral and intervention.

Gender also emerged as a significant factor in alexithymia prevalence, with a higher proportion of female adolescents affected-contrary to general population trends that associate alexithymia more frequently with males (27). Previous findings in adolescents have been inconsistent, with some studies reporting higher rates among females (28) and others showing no gender difference. One study specifically reported a higher prevalence of alexithymic traits in girls with abdominal OB (29), aligning with our findings of a female predominance in the severely obese subgroup.

Additionally, research from Türkiye supports the notion that alexithymia in adolescents is associated with various psychopathological indicators. Studies have shown that alexithymia is linked to high levels of anxiety and is mediated by thought-action fusion (30). It increases the risk of being subjected to peer bullying when combined with behavioral problems (31). It may serve as a risk factor for somatization (32). Moreover, problematic social media use is positively correlated with alexithymia in this age group (33), and adolescents with conversion disorder in the form of psychogenic seizures show elevated alexithymia and lower self-esteem levels (34). These findings collectively underscore the critical role of alexithymia as a comorbid vulnerability in adolescent mental health, particularly in populations with OB.

Despite exploring a range of laboratory parameters, including HOMA-IR, serum lipid profiles, and transaminases, our study did not

detect significant associations with alexithymia. This suggests that alexithymia may precede metabolic dysfunctions or represent a parallel psychosomatic process rather than a downstream effect.

### Study Limitations

The results should be interpreted in the context of several limitations. The fact that the study was conducted on patients who applied to the hospital limits the generalizability of the results to the broader society. However, considering that patients with OB who apply to the hospital may be more likely to need help than those who do not, it is important to allocate resources accordingly. This hypothesis is further supported by the lower number of patients with OW in the study. Yet we believe that our study will enhance the subject matter and open new avenues for future research by introducing a unique perspective to the existing literature. It's crucial to recognize the limitations of the study's design. While it provides valuable statistical data, it doesn't allow us to establish causality with certainty. A prospective design would have offered even more insightful information. Another limitation is the lack of clinical assessment for alexithymia, as it was solely measured through a self-report scale, which could have potentially induced bias in the results. However, the TAS-20 scale is the most widely used and dependable tool for identifying and defining alexithymia (13).

## Conclusion

The current study highlights that body fat percentage may be a valuable tool for identifying alexithymia in adolescents with OW and OB. Moreover, being female and having a higher WHtR may also play an instrumental role in this connection.

### Ethics

**Ethics Committee Approval:** The study was reviewed by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2023/02-14, date: 22.02.2023) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

**Informed Consent:** Both verbal and written informed consent was collected from all participants and their parents.

### Footnotes

**Authorship Contributions:** Concept - N.K.; Design - N.K.; Data Collection or Processing - M.E.U., Ö.K.; Analysis or Interpretation – N.K., H.Ş., Ö.K.; Literature Search - N.K., H.Ş.; Writing – N.K., H.Ş., M.E.U.

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

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# Diagnostic Efficacy of Transthoracic Fine Needle Aspiration Biopsy in Lung Lesions and Comparative Evaluation of Complications with the Literature

Mehmet Karagülle[1], Mehmet Semih Çakır[2], Mehmet Kurt[1], Burcu Özcan[3], Abdullah Soydan Mahmutoglu[4]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Radiology, İstanbul, Türkiye
[2]İstanbul University Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, İstanbul Education and Research Hospital, Clinic of Pathology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Education and Research Hospital, Clinic of Radiology, İstanbul, Türkiye

## ABSTRACT

**Introduction:** We aim to examine the diagnostic accuracy and complication profile of computed tomography (CT)-guided transthoracic fine needle aspiration biopsy (TTFNAB) in patients presenting with pulmonary lesions, while also reviewing these outcomes in light of current literature.

**Methods:** This retrospective study included 102 patients who underwent CT-guided TTFNAB between April 2020 and June 2022 at a tertiary care center. All procedures were carried out by three radiologists, each possessing a minimum of two years of experience in the field of interventional radiology. Diagnostic yield, complication rates (pneumothorax, hemorrhage, hemoptysis), and lesion characteristics were recorded. Results were statistically analyzed and compared with recent literature.

**Results:** TTFNAB provided a diagnostic yield of 98%. Malignancy was detected in 76.5% of cases, with adenocarcinoma and squamous cell carcinoma being the most common subtypes. Pneumothorax occurred in 12.7% of cases, tract-perilesional hemorrhage in 21.6%, and hemoptysis in 2%. Lesions located away from the pleura had significantly higher pneumothorax and bleeding rates ($p=0.013$ and $p=0.0005$, respectively). No significant correlation was found between complication rates and gender, lesion location, presence of emphysema, or procedure position.

**Conclusion:** CT-guided TTFNAB is a highly effective and relatively safe diagnostic tool for lung lesions. While complication rates are acceptable, lesion proximity to the pleura significantly influences risk. Findings are consistent with the literature and support the continued use of TTFNAB in appropriate clinical settings.

**Keywords:** Computed tomography, transthoracic lung biopsy, fine-needle aspiration biopsy, pneumothorax

## Introduction

Lung lesions are commonly seen in clinical settings, and accurate histopathological diagnosis is essential for appropriate management. Among image-guided biopsy techniques, computed tomography (CT)-guided transthoracic fine needle aspiration biopsy (TTFNAB) remains a widely used method because of its non-invasive approach and excellent diagnostic accuracy, particularly in the evaluation of suspected malignancies. Compared to core biopsy techniques, TTFNAB offers the advantage of reduced complication risks due to the use of thinner needles (1). However, concerns remain regarding sample adequacy and diagnostic reliability. The aim of this study is to evaluate the diagnostic effectiveness and complication profile of TTFNAB in a series of patients with lung lesions, as well as to analyze these outcomes in the context of recent literature.

## Methods

Lung biopsies performed between April 2020 and June 2022 were retrospectively reviewed, and all participants provided informed consent. The study was approved by the University of Health Sciences Türkiye, İstanbul Education and Research Hospital, Clinical Research Ethics Committee (approval number: 202, date: 17.06.2022). The study included patients with non-diagnostic bronchoscopic biopsy results and those unsuitable for bronchoscopy. These patients were referred for transthoracic biopsy. Patients were excluded if they had lesions smaller than 5 mm, suspected vascular

**Address for Correspondence:** Mehmet Karagülle MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Radiology, İstanbul, Türkiye
**E-mail:** mhmtkrglle@gmail.com **ORCID ID:** orcid.org/0000-0002-1631-8975

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lesions, uncorrectable coagulopathy [international normalized ratio (INR) >1.5 or platelet (PLT) <50,000], inability to comply with biopsy positioning, or failure to discontinue anticoagulant/antiplatelet medications 3-7 days prior to the intervention. A total of 102 patients were included in the study. In our study, the biopsy procedure could not be performed in only one patient due to an inability to position the patient properly because of scoliosis. Therefore, this patient was excluded from the study. All biopsies were carried out with a Toshiba Aquilion 128-slice CT scanner by three different radiologists, each possessing a minimum of two years of experience in interventional radiology. Based on prior thoracic CT images, patients were positioned in prone, supine, or lateral decubitus positions to optimize the shortest and safest access to the lesion. To determine the biopsy trajectory, metallic markers were placed on the patient's skin, and a pre-biopsy CT scan was performed using 20 mAs, 120 kV, and a slice thickness of 5 mm. The biopsy needle entry site was identified and marked. After disinfecting the area with povidone-iodine, 2% lidocaine was administered for local anesthesia. A 22G fine needle (Egemen TMT) was used in all procedures. During the procedure, CT imaging was used to confirm the correct placement of the needle within the lesion. Patients were instructed to hold their breath for the duration of the procedure. Aspiration was performed, and the needle was withdrawn along the same trajectory.

The adequacy of the aspirated material was immediately evaluated in the procedure room by a cytopathologist. In cases where the sample was considered to lack sufficient cellularity for diagnosis, a second aspiration biopsy was performed in some patients upon the recommendation of the cytopathologist and approval of the interventional radiologist.

Post-procedural thoracic CT scans were performed to assess complications such as pneumothorax or bleeding. Small pneumothorax cases were managed conservatively with 4-6 days of radiographic follow-up, while large ones (greater than 3 cm or involving more than 30% of the hemithorax) required chest tube drainage and 24-hour hospital observation. CT-guided TTFNAB samples are presented in Figure 1. Lesion size was measured based on the longest axis on CT, and diagnostic adequacy was determined according to pathology reports. Patients without pathology reports were excluded from the study.

### Statistical Analysis

Statistical analyses were conducted using SPSS 23.0 (IBM). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequency and percentage. Group comparisons were performed using the chi-square test, Fisher's exact test, t-test, and Mann-Whitney U test, with a statistical significance threshold set at $p<0.05$.

## Results

A total of 102 patients were included, of whom 78 were male and 24 were female, with a mean age of 63±11.52 years. The average lesion size was 30.08 mm. The majority of lesions were found in the upper lobes of the lungs. Demographic data, lesion characteristics, and statistical values are presented in Table 1. Pathological analysis revealed a diagnostic yield of 98%. Malignant diagnoses included adenocarcinoma (23.5%), squamous cell carcinoma (23.5%), and metastases (13.7%) (Table 2). Pneumothorax occurred in 12.7% (13 patients). Only 1 required chest tube insertion. Tract-perilesional hemorrhage was observed in 21.6% (22 patients). Hemoptysis occurred in 2 percent of patients (2 patients). No complications were reported in 63.7% of cases. In patients who developed pneumothorax, one out of 13 in the TTFNAB required chest tube insertion and was monitored in the hospital for at least 24 hours. All other complications resolved spontaneously after follow-up without the need for hospitalization. Pneumothorax was significantly more common in lesions not in contact with the pleura (p=0.013). Regarding the average pleural lesion distance, the TTFNAB group had a p-value of 0.085.

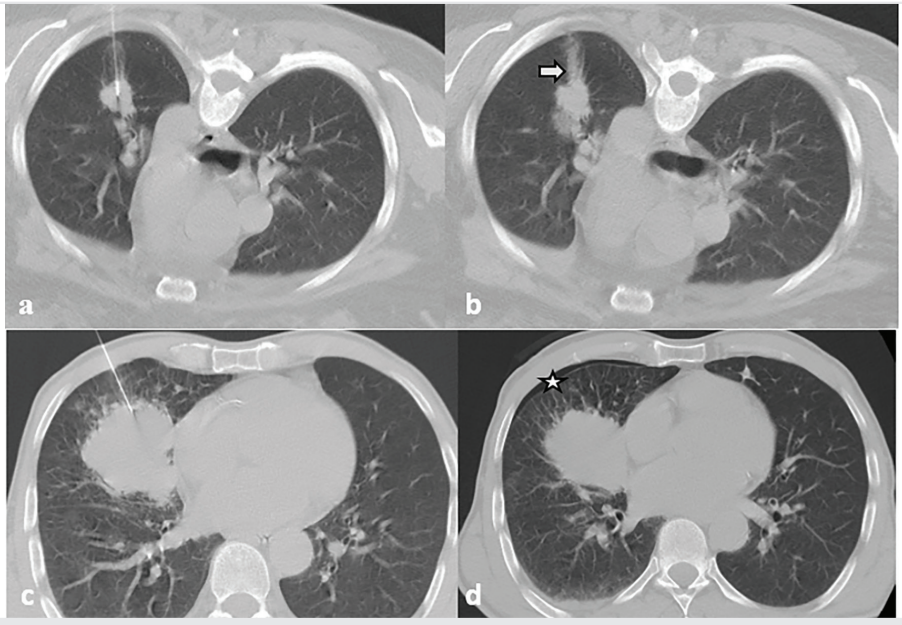



**Figure 1.** TTFNAB samples in images (a, c) tract and perilesional hemorrhage complications are indicated by the thick, outlined white arrow in image (b) pneumothorax complication samples are marked with a star in image d.
TTFNAB: Transthoracic fine needle aspiration biopsy

**Table 1. Demographic data lesion characteristics, and statistical values**

| | TTFNAB |
|---|---|
| Age (years) | 63 (SD = +/- 11.52) min.:36/-max.:88 |
| Sex<br>Female<br>Male | <br>24<br>78 |
| Lesion locations<br>Right upper lobe<br>Right middle lobe<br>Right lower lobe<br>Left upper lobe<br>Left lower lobe | <br>27<br>5<br>13<br>34<br>23 |
| Patient positioning during procedure<br>Lateral decubitis<br>Supine<br>Prone | <br>14<br>26<br>62 |
| Transfissural access<br>Yes<br>No | <br>21<br>81 |
| Emphysema<br>Yes<br>No | <br>41<br>61 |
| Pneumotorax<br>Yes<br>No | <br>13<br>89 |
| PX Treatment<br>Thorax tube<br>Follow | <br>1<br>12 |
| Pathology<br>Benign<br>Atypia<br>Malignant<br>Nondiagnostic | <br>18<br>4<br>78<br>2 |
| Hemorrhage<br>Yes<br>No | <br>22<br>80 |
| Hemoptysis<br>Yes<br>No | <br>2<br>100 |
| Lesion Characteristics<br>Solid<br>Semisolid<br>Ground glass | <br>83<br>16<br>3 |
| Cavitations<br>Yes<br>No | <br>26<br>76 |
| Calcifications<br>Yes<br>No | <br>13<br>89 |
| Air bronchogram<br>Yes<br>No | <br>19<br>83 |
| Average lesion size | 30.08 mm (SD =15.35) (min.:9 mm max.:100 mm) |
| Lesion-pleura relation<br>Pleura based<br>Distant from pleura | <br>42<br>60 |
| Average lesion-pleura distance | 14.1 mm SD =13.71 (min.:0 max.: 41 mm) |

TTFNAB: Transthoracic fine needle aspiration biopsy, SD: Standard deviation, Min.: Minimum, Max.: Maximum

**Table 2. Pathological findings**

| Pathological daignosis | TTFNAB | Rate (%) |
|---|---|---|
| Adenocarcinoma | 24 | 23.53 |
| Squamous cell cancer | 24 | 23.53 |
| Small cell lung cancer | 4 | 3.92 |
| Non-small cell lung cancer | 4 | 3.92 |
| Metastasis | 14 | 13.73 |
| Inflamatory findings | 8 | 7.84 |
| Atypical cell | 4 | 3.92 |
| Granulomatous reaction | 2 | 1.96 |
| Neuroendocrine tumor | 1 | 0.98 |
| Lung parencyhma and blood cells | 4 | 3.92 |
| Non-diagnostic material | 2 | 1.96 |
| Hamartoma | 2 | 1.96 |
| B-cell lymphoma | 2 | 1.96 |
| Giant cell pleomorphic sarcoma | 1 | 0.98 |
| Spindle cell carcinoma | 2 | 1.96 |
| Solitary fibrous tumor | 2 | 1.96 |
| Pleomorphic Rhabdomyosarcoma | 2 | 1.96 |

TTFNAB: Transthoracic fine needle aspiration biopsy

Although this result did not reach statistical significance, it was close to the conventional threshold, suggesting a potential association. In TTFNAB patients, no statistically significant association was observed between pneumothorax complications and gender, lesion location, presence of emphysema, transfissural access, patient position during the procedure, average number of biopsies, and average lesion size ($p>0.05$) (Table 3).

In terms of tract-perilesional hemorrhagic complications, bleeding was observed more frequently in lesions not located on the pleura compared to pleural-based lesions; and this difference was statistically significant ($p=0.0005$). Similarly, as the average pleural distance increased, the incidence of tract-perilesional bleeding also increased significantly ($p=0.0004$). Although an increasing trend in hemorrhagic complications was observed with a higher number of biopsies, this was not statistically significant ($p=0.158$). Furthermore, no statistically significant association was found between tract-perilesional bleeding and gender, lesion location, presence of emphysema, transfissural access, patient position, or lesion size ($p>0.05$) (Table 4).

## Discussion

CT-guided TTFNAB is a widely used and reliable method in the diagnosis of pulmonary lesions due to its high diagnostic accuracy and acceptable complication profile (2). It is especially preferred in cases when bronchoscopic access is not possible, in newly developing or enlarging nodules and masses, in patients with multiple nodules, or in those with persistent infiltrative lung disease where diagnostic yield cannot be obtained through sputum culture or bronchial lavage. It is also effective

**Table 3. The statistical relation between cases with pneumothorax complications and other clinical or procedural findings**

| | | TTFNAB | | | |
|---|---|---|---|---|---|
| | | Pneumotorax | | | |
| | | Yes | No | Total | p |
| Sex | Male | 8 | 70 | 78 | p=0.31 |
| | Female | 5 | 19 | 24 | |
| Lesion locations | Right upper lobe | 6 | 21 | 27 | |
| | Right middle lobe | 0 | 5 | 5 | |
| | Right lower lobe | 1 | 12 | 13 | p=0.45 |
| | Left upper lobe | 3 | 31 | 34 | |
| | Left lower lobe | 3 | 20 | 23 | |
| Lesion-pleura relation | Pleura based | 1 | 39 | 40 | p=0.013 |
| | Distant from pleura | 12 | 50 | 62 | |
| Emphysema | Yes | 5 | 36 | 41 | p=0.89 |
| | No | 8 | 53 | 61 | |
| Transfissural access | Yes | 4 | 17 | 21 | p=0.33 |
| | No | 9 | 72 | 81 | |
| Patient positioning during procedure | Lateral decubitis | 1 | 13 | 14 | |
| | Supine | 6 | 20 | 26 | p=0.143 |
| | Prone | 6 | 56 | 62 | |
| Average lesion-pleura distance (mm) | | 19.62 mm (SD =9.97) | 13.29 mm (SD =14.03) | 14.1 mm (SD =13.71) | p=0.085 |
| Average number of biopsies | | 1.62 (SD =0.5) | 1.46 (SD =0.5) | 1.48 (SD =0.5) | p=0.458 |
| Average lesion size (mm) | | 27.31 mm (SD =21.15) | 30.48 mm (SD =14.42) | 30.08 mm (SD =15.35) | p=0.187 |

TTFNAB: Transthoracic fine needle aspiration biopsy, SD: Standard deviation

**Table 4. The statistical relation between cases with tract-perilesional hemorrhage complications and other findings**

| | | TTFNAB | | | |
|---|---|---|---|---|---|
| | | Tract-perilesional hemorrhage | | | |
| | | Yes | No | Total | p |
| Sex | Male | 18 | 60 | 78 | p=1 |
| | Female | 4 | 20 | 24 | |
| Lesion localisations | Right upper lobe | 8 | 19 | 27 | |
| | Right middle lobe | 0 | 5 | 5 | |
| | Right lower lobe | 4 | 9 | 13 | p=0.46 |
| | Left upper lobe | 6 | 28 | 34 | |
| | Left lower lobe | 4 | 19 | 23 | |
| Lesions-pleura relation | Pleura based | 2 | 38 | 40 | p=0.0005 |
| | Distant from pleura | 20 | 42 | 62 | |
| Emphysema | Yes | 9 | 32 | 41 | p=0.947 |
| | No | 13 | 48 | 61 | |
| Transfisurral access | Yes | 8 | 13 | 21 | p=0.53 |
| | No | 14 | 67 | 81 | |
| Patient positioning during procedure | Lateral decubitis | 3 | 11 | 14 | |
| | Supine | 6 | 20 | 26 | p=0.93 |
| | Prone | 12 | 50 | 62 | |
| Average lesion-pleura distance (mm) | | 26.41 mm (SD =12.29) | 10.71 mm (SD =12.09) | 14.1 mm (SD =13.71) | p=0.0004 |
| Average number of biopsies | | 1.64 (SD =0.49) | 1.43 (SD =0.5) | 1.48 (SD =0.5) | p=0.158 |
| Average lesion size (mm) | | 27.77 mm (SD =14.14) | 30.87 mm (SD =15.72) | 30.08 mm (SD =15.35) | p=0.381 |

TTFNAB: Transthoracic fine needle aspiration biopsy, SD: Standard deviation

in diagnosing hilar lesions inaccessible via bronchoscopy and chest wall masses. However, TTFNAB is contraindicated in certain clinical scenarios such as severe coagulopathy (PLTs <50,000/mm³, INR >1.5), the need for mechanical ventilation, advanced chronic obstructive pulmonary disease, severe pulmonary hypertension, patient non-cooperation during the procedure and vascular lesions (2,3).

In our study, the diagnostic accuracy of TTFNAB was found to be 98%. This rate is higher than the findings of Yao et al. (4), who reported a diagnostic yield of 78.9%, and Heyer et al. (5), who reported 82%. The presence of a pathologist during TTFNAB procedures, enabling immediate evaluation of the specimen, providing feedback on its adequacy, and allowing for repetition of the procedure if necessary, increases the diagnostic yield (6,7). In a study by Santambrogio et al. (8), the diagnostic rate was found to be higher in cases where a pathologist was present during the biopsy compared to those performed without a pathologist. In our study, a cytopathologist was present during all TTFNAB procedures, allowing for immediate evaluation of the samples. Repeat biopsies were performed when necessary. We believe that this practice may have contributed to the high diagnostic accuracy.

One of the most prevalent complications associated with TTFNAB is pneumothorax. Its incidence has been reported to range between 10% and 45% in the literature (9). In our study, the pneumothorax rate was 12.7%, consistent with previous findings. Factors believed to elevate the risk of pneumothorax include small lesion size, deep lesion location, lower lobe involvement, inability of elderly patients to hold their breath, fissure penetration, and presence of emphysema (9,10). However, in this study, no significant correlation was observed between pneumothorax and variables such as gender, lesion location, presence of emphysema, transfissural approach, patient positioning, number of biopsy passes, or lesion size. In both this study and the literature, the absence of pleural contact and greater pleural-lesion distance were associated with higher complication risk (11,12).

In cases of pneumothorax larger than 3 cm or accompanied by symptoms such as acute chest pain and dyspnea, needle aspiration or chest tube drainage is recommended (2). The rate of pneumothorax requiring treatment is reported to range between 3% and 15% in the literature (3). In our study, this rate was only 1%, which may reflect careful procedural planning and execution. Advancing the needle during breath-holding, avoiding fissures, bullae, and blebs, and minimizing the needle path length through lung parenchyma are considered effective strategies to prevent pneumothorax (13).

Tract-perilesional hemorrhage is another common complication, reported in 5% to 27% of cases in the literature (14,15). In our study, the incidence was 21.6%, aligning with previous reports. The depth of the lesion has been determined to be the most significant risk factor for hemorrhage (3). In our study, the mean lesion depth in patients who developed hemorrhage was 26.41 mm, compared to 10.71 mm in those who did not, highlighting a significant difference. To minimize the likelihood of pulmonary hemorrhage, it is recommended that patients be placed in the lateral decubitus position with the biopsy side facing down after the procedure (2). In our series, all hemorrhagic events resolved spontaneously without requiring additional intervention, and none were clinically severe.

Other rare but serious complications include systemic air embolism, pericardial tamponade, and hemothorax, which carry high morbidity and mortality and require a multidisciplinary approach. The mortality rate of such events has been reported to be below 1% in the literature (2). In our patient group, no cases of mortality or major complications were observed.

### Study Limitations

This study has a number of limitations. First, its retrospective nature and the limited sample size may restrict the applicability of the findings. The lack of long-term follow-up and absence of surgical outcomes prevents definitive conclusions regarding final diagnoses. Although the procedures were performed at a single center by three different operators, all radiological assessments were conducted by the same radiologist. Cytological evaluations were also performed by the same cytopathologist, which may affect generalizability.

Additionally, because of the small sample size of patients with emphysema and the absence of variation in emphysema types, an objective scoring system such as the Goddard score could not be applied. Therefore, the likelihood of pneumothorax in patients with emphysema was presented independently of emphysema severity.

## Conclusion

Our study demonstrates that TTFNAB, when performed by experienced operators with cytopathological support, is a safe diagnostic method with high accuracy and generally mild, manageable complications. Absence of pleural contact and increased pleural-lesion distance were associated with higher complication rates. TTFNAB remains a valuable tool in the clinical assessment of peripheral, high-risk, or bronchoscopically inaccessible lung lesions. Future research should involve larger patient populations and include prospective, randomized controlled trials. Repeating similar studies in different centers with different operators and cytopathologists would enhance generalizability and minimize potential biases.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, İstanbul Education and Research Hospital, Clinical Research Ethics Committee (approval number: 202, date: 17.06.2022).

**Informed Consent:** All participants provided informed consent.

### Footnotes

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

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# The Relationship Between Changes in the Neutrophil-Lymphocyte Ratio (NLR) and Radiological Progression in Cervical Cancer

Rumeysa Çolak[1], İlkay Gültürk[2], Ezgi Değerli[1], Caner Kapar[1], Seher Yıldız Tacar[1], Mesut Yılmaz[1]

[1]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

## ABSTRACT

**Introduction:** Peripheral counts of neutrophils and lymphocytes and their changes have been associated with disease prognosis in various malignancies. While several studies have investigated the changes and clinical implications of the peripheral blood neutrophil to lymphocyte ratio (NLR) in cervical cancer, the prognostic value of NLR, in locally advanced cervical cancer remains unclear.

**Methods:** A retrospective analysis of cervical cancer patients who received definitive chemoradiotherapy (CRT) was carried out. NLR values were identified pre-CRT and post-CRT, and changes in these values were calculated. We assessed the relationship between changes in the NLR and clinicopathological features and disease prognosis.

**Results:** A total of eighty-five patients with locally advanced cervical cancer who received CRT were analyzed in this study. The rate of decrease in NLR in patients with progression was 22.2%, while in patients without progression was 17.2%. The rate of increase in NLR in patients with progression was 77.8%, while in patients without progression it was 82.8%. Higher or lower NLR levels were not found to have a significant relationship with disease progression (p=0.584).

**Conclusion:** The impact of changes in NLR on the prognosis of cervical cancer patients needs further validation in multicenter studies.

**Keywords:** Cervical cancer, definitive chemoradiotherapy, neutrophil-to-lymphocyte ratio, prognosis

## Introduction

Cervical cancer has the highest mortality rate among gynecological diseases and is one of the most common tumors affecting women globally. Cervical cancer is still a leading cause of death among women, despite modern treatments, mainly due to late diagnosis or insufficient early screening (1). For individuals with locally advanced cervical cancer, the standard treatment is concurrent chemoradiotherapy (CRT) using cisplatin. It is essential to predict the prognosis of patients to improve the standards of care and apply more intensive therapies.

In recent years, changes in peripheral blood indicators, such as variations in neutrophil and lymphocyte numbers, have been linked to tumorigenesis and disease prognosis (2). Although a change in the neutrophil-to-lymphocyte ratio (NLR) is strongly associated with the patient's prognosis, its prognostic significance in locally advanced cervical cancer is yet unknown.

Chemotherapy and radiotherapy (RT) may stimulate tumor-specific cellular immune responses and affect immune suppression in the tumor microenvironment (3). Most clinical investigations have studied the baseline neutrophil and lymphocyte counts as prognostic indicators of treatment outcomes (4,5). Since the immune system is in a dynamic state that can be altered by chemotherapy and radiation, employing dynamic alterations of NLR rather than a single time-point NLR may provide more information.

Research has demonstrated that survival outcomes in different solid tumors are correlated with increasing pre-treatment NLR, post-treatment NLR, and the change in NLR. However, according to some research, pre-treatment NLR has no relationship to prognosis, whereas post-treatment NLR predicts progression-free survival (PFS) (6,7). In this context, the prognostic relevance of the changes in NLR requires additional examination.

**Address for Correspondence:** Rumeysa Çolak MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye
**E-mail:** colak.rmys@gmail.com **ORCID ID:** orcid.org/0000-0002-3867-0793

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The majority of research on prognostic hematologic markers in cervical cancer has highlighted the critical role of pretreatment NLR, underscoring its significance in patient outcomes. The impact of CRT on hematological parameters during treatment in patients with cervical cancer has not yet been established.

We conducted this study to assess whether the dynamic changes in NLR could serve as a prognostic indicator for patients with locally advanced cervical cancer undergoing definitive CRT. By identifying this relationship, we aim to improve clinical outcomes and provide valuable insights for developing effective treatment strategies.

## Methods

Eighty-five patients with locally advanced cervical cancer who had definitive CRT between 2016 and 2023 were included in a retrospective, single-center analysis. The clinical staging criteria of the International Federation of Gynecology and Obstetrics (FIGO) were used to categorize the patients.

This study included patients aged 18 and above who had been diagnosed with cervical cancer through histopathological analysis and had undergone treatment with both RT and chemotherapy. Additionally, patients who had distant metastases, those diagnosed with another tumor within the last three months, or those whose clinical or laboratory data were unavailable, were not included in the study.

In this group, patients received weekly doses of cisplatin along with an efficient pelvic chemoradiation treatment regimen that delivered a total dose of 50 Gy in 25 fractions over 5 weeks. Some patients received brachytherapy.

Clinical and pathological features, comorbidities, and laboratory data were collected from the hospital's information system. Comprehensive blood cell counts, along with differential counts, were conducted at baseline before treatment and again 5 to 6 weeks after the conclusion of CRT. By allowing time between the conclusion of treatment and blood test extraction, we significantly reduce the risk of myelotoxicity, primarily associated with chemotherapy. The ratio of absolute neutrophil to absolute lymphocyte counts in the blood sample was used to compute the NLR before and after therapy. The NLR change percentage was determined as 10% according to ROC analysis. Increased NLR was defined as a $^{3}$10% elevation, and decreased NLR was defined as a $^{3}$10% reduction.

The final follow-up occurred in October 2024. For the first two years following therapy, all patients were assessed every three months; after that, they were reviewed every six months. The follow-up examination included, among other things, a blood test, pelvic magnetic resonance imaging, chest radiography, and a gynecological physical examination. When cancer returns to the primary tumor site or to the regional lymph nodes in the pelvic or para-aortic regions, it is referred to as locoregional recurrence. A disease recurrence outside the pelvic or para-aortic areas that is verified by pathological or radiological evidence is referred to as distant metastasis. Disease-free survival (DFS) measures the time from a patient's definitive diagnosis to the recurrence or metastasis of the disease.

The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-05-17, date: 18.03.2024). Because the study was carried out retrospectively and participant confidentiality was guaranteed, informed consent was not required.

### Statistical Analysis

The descriptive statistics of the data include mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of variables. The independent sample t-test was used to analyze quantitative independent data with a normal distribution. The Mann-Whitney U test was utilized to analyze independent quantitative data with a non-normal distribution. The chi-square test was employed to analyze independent qualitative data. Kaplan-Meier was used in the survival analysis. The SPSS 28.0 program was used in the analyses.

## Results

Following a thorough screening, 85 patients were included in this study, with ages ranging from 33 to 77 years. The average patient age was 53.3±11.4 years. The median follow-up period was 37.1 months. According to the FIGO Criteria for cervical cancer, five patients were identified as having clinical stage I, 35 as clinical stage II, and 45 as clinical stage III. Eastern Cooperative Oncology Group, performance score (ECOG) was 0 in 68 patients and 1 in 17 patients. In terms of pathological types, there were 78 patients diagnosed with squamous carcinoma and seven patients diagnosed with adenocarcinoma. The tumor size ranged from 2 to 11 cm, with a median of 4.6 cm. There were 24 and 64 patients with and without involvement of parametrial tissue, respectively. Lymph node metastasis was detected in 37 patients. 82.4% of patients received pelvic RT, and 17.6% received pelvic and paraaortic RT. Additionally, brachytherapy was performed in 85.9% of the patients. All patients received concurrent chemotherapy. Cisplatin was the only chemotherapeutic agent used during RT. 89.4% of the patients received 40 mg/m$^2$ cisplatin, while 10.6% received 25 mg/m$^2$ (Table 1).

The mean pretreatment NLR was 3.4±2.5, while the mean posttreatment NLR was 6.3±5.6. There was an increase in NLR in 81.2% of patients and a decrease in NLR in 18.8% (Table 1). The median DFS was 54.1 months.

There was local/locoregional or distant metastasis in 27 patients (31.8%). We classified the patients into two groups according to their progression status. The patients' ages did not differ significantly (p=0.035) between the groups with and without progression. ECOG score, histology, tumor size, parametrium involvement, lymph node metastasis, and FIGO stage did not differ significantly (p=0.351, p=0.132, p=1.00, p=0.175, p=0.127, respectively) between the groups with and without progression. There was no statistical difference in these groups in terms of RT area, whether they received brachytherapy, or platinum doses (p=0.886, p=0.900, p=0.516). The median follow-up was similar (p=0.278) (Table 2).

We analyzed the impact of pretreatment, and post-treatment NLR levels and their change on progression. The pretreatment NLR was 3.8±3.4 in patients with progression and 3.2±1.9 in those without progression.

There was no statistically significant difference (p=0.543). Post-treatment NLR was 6.5±4.5 in the patients with progression and 6.3±6.1 in those without progression. There was no statistically significant difference (p=0.637). The rate of decrease in NLR in patients with progression was 22.2%, while in patients without progression it was 17.2%. There was no statistically significant difference between them. The rate of increase in NLR in patients with progression was 77.8%, while in patients without progression it was 82.8%. There was no statistical significance between them (p=0.584) (Table 2).

DFS was 49.9 months in patients with decreased NLR and 54.8 months in those with increased NLR. No statistically significant difference was found between the two groups (p=0.510) (Figure 1).

## Discussion

In addition to its role in tumoral surveillance, the immune system plays a crucial part in cancer development, as it can create an inflammatory environment and facilitate tumor proliferation (8). Since inflammation linked to cancer is one of its distinguishing features, comprehending the host's immunological and inflammatory states is crucial, as inflammation is essential for the development and progression of tumors (9). Extensive research has demonstrated that inflammatory responses are fundamental to the processes of cancer development, invasion, metastasis, and tumorigenesis across various cancer types (10).

These characteristics can be assessed using cost-effective and easily repeatable indicators from peripheral blood samples. The NLR is one of the most extensively researched inflammation-based indices. Tumor growth is thought to be significantly influenced by neutrophils and lymphocytes. While lymphocytes serve as the primary antitumor cells, neutrophils produce pro-inflammatory mediators that suppress other immune cells' cytolytic function and facilitate cancer onset and advancement (11).

Peripheral blood NLR has emerged as a research focus in recent years due to its superior prognostic and predictive value in various tumors, including renal cell carcinoma (12), intrahepatic cholangiocarcinoma (13), esophageal cancer (14), and colorectal cancer (15).

Numerous studies exclusively examined the pretreatment values of inflammatory markers.

One study indicated that increased pretreatment NLR levels were substantially correlated with worse survival (16). On the other hand, DFS and overall survival (OS) did not significantly differ between patients

**Table 1. Patient characteristics**

| | | Min.-Max. | | | Median | Mean ± SD/n=% | | |
|---|---|---|---|---|---|---|---|---|
| Age (years) | | 33.3 | - | 77.3 | 52.0 | 53.3 | ± | 11.4 |
| ECOG-PS | 0 | | | | | 68 | | 80.0% |
| | I | | | | | 17 | | 20.0% |
| Histology | SCC | | | | | 78 | | 91.8% |
| | Adenocarcinoma | | | | | 7 | | 8.2% |
| Tumor size (cm) | | 2.0 | - | 11.0 | 4.6 | 4.6 | ± | 1.4 |
| Parametrium involvement | (-) | | | | | 24 | | 28.2% |
| | (+) | | | | | 61 | | 71.8% |
| Lymph node metastasis | (-) | | | | | 48 | | 56.5% |
| | (+) | | | | | 37 | | 43.5% |
| FIGO stage | I | | | | | 5 | | 5.9% |
| | II | | | | | 35 | | 41.2% |
| | III | | | | | 45 | | 52.9% |
| RT field | Pelvic<br>Pelvic + paraaortic | | | | | 70<br>15 | | 82.4%<br>17.6% |
| Brachytherapy | (-)<br>(+) | | | | | 12<br>73 | | 14.1%<br>85.9% |
| CRT platine dose | 25 mg/m$^2$<br>40 mg/m$^2$ | | | | | 9<br>76 | | 10.6%<br>89.4% |
| Progresyon | (-)<br>(+) | | | | | 58<br>27 | | 68.2%<br>31.8% |
| NLR | | | | | | | | |
| Pretreatment | | 1.1 | - | 18.5 | 2.8 | 3.4 | ± | 2.5 |
| Posttreatment | | 0.7 | - | 43.0 | 4.7 | 6.3 | ± | 5.6 |
| Decresed NLR<br>Incresed NLR | | | | | | 16<br>69 | | 18.8%<br>81.2% |

ECOG-PS: Eastern Cooperative Oncology Group, performance score, NLR: Neutrophil-lymphocyte ratio, CRT: Chemoradiotherapy, RT: Radiotherapy, FIGO: International Federation of Gynecology and Obstetric, Min.: Minimum, Max.: Maximum, SD: Standard deviation, SCC: Squamous cell carcinoma

with high and low NLR, in another trial (17). This finding underscores the complexity of patient outcomes and highlights the need to understand these factors more thoroughly. We also found no significant relationship between patients' pretreatment or post-treatment NLR and survival outcomes. One reason for the difference in these findings may be the variety of the NLR cutoff value.

Many studies have explored the dynamic changes in various markers that could reveal the delicate balance between the host's immune response and inflammation. The clinical and cutoff values of the change in NLR in relation to cervical cancer are still a topic of controversy, even though a limited number of studies have reported on its clinical prognostic value. In one trial, it was observed that a change in NLR, particularly after the third week of treatment, may be indicative of the treatment outcomes, of definitive CRT for cervical cancer patients (18).

Trinh et al. (19) revealed an association between elevated NLR levels post-treatment and significantly poorer outcomes in both PFS and OS. This finding highlights the importance of monitoring NLR as a potential prognostic marker for patients. While LMR pre- and post-treatment were positively correlated with PFS, an increase in LMR during CRT was negatively correlated with PFS and OS. In various studies, it has been demonstrated that patients with cervical cancer who present a high preoperative NLR face markedly poorer OS and PFS compared to their counterparts. This highlights the critical importance of monitoring NLR levels in preoperative assessments to better predict patient outcomes and tailor treatment strategies effectively. However, no prognostic difference was noted between the groups with elevated and reduced NLR (20). In our study, we found no clinical difference between patients with increased and decreased NLR in terms of prognosis. This outcome is expected, as NLR is a dynamic indicator that is susceptible to the host's condition, and inflammation, the administered treatment, and the resultant response. In addition, the small sample size may have influenced these results. In this context, we believe blood biomarkers, including NLR, need a prospective investigation in randomized clinical trials.

**Table 2. The relationship between clinical parameters and NLR change with progression**

| | | Progression (-) (n=58) | | | | Progression (+) (n=27) | | | | p | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean ± SD/n-% | | | Median | Mean ± SD/n-% | | | Median | | |
| Age (years) | | 51.6 | ± | 11.7 | 48.8 | 56.7 | ± | 9.8 | 57.3 | 0.035 | m |
| ECOG-PS | 0 | 48 | | 82.8% | | 20 | | 74.1% | 68 | 0.351 | $X^2$ |
| | I | 10 | | 17.2% | | 7 | | 25.9% | 17 | | |
| Histology | SCC | 55 | | 94.8% | | 23 | | 85.2% | 78 | 0.132 | $X^2$ |
| | Adenocarcinoma | 3 | | 5.2% | | 4 | | 14.8% | 7 | | |
| Tumor size (cm) | | 4.7 | ± | 1.5 | 4.6 | 4.6 | ± | 1.2 | 4.5 | 1.000 | m |
| Parametrium involvement | (-) | 19 | | 32.8% | | 5 | | 18.5% | 24 | 0.175 | $X^2$ |
| | (+) | 39 | | 67.2% | | 22 | | 81.5% | 61 | | |
| Lymph node metastasis | (-) | 36 | | 62.1% | | 12 | | 44.4% | 48 | 0.127 | $X^2$ |
| | (+) | 22 | | 37.9% | | 15 | | 55.6% | 37 | | |
| FIGO stage | IB | 3 | | 5.2% | | 2 | | 7.4% | 5 | 0.426 | $X^2$ |
| | IIB | 26 | | 45.0% | | 9 | | 33.3% | 23 | | |
| | IVA | 29 | | 50.0% | | 16 | | 59.2% | 30 | | |
| **RT field** | | | | | | | | | | | |
| Pelvic | | 48 | | 82.8% | | 22 | | 81.5% | 70 | 0.886 | $X^2$ |
| Pelvic + paraaortic | | 10 | | 17.2% | | 5 | | 18.5% | 15 | | |
| Brachytherapy | (-) | 8 | | 13.8% | | 4 | | 14.8% | 12 | 0.900 | $X^2$ |
| | (+) | 50 | | 86.2% | | 23 | | 85.2% | 73 | | |
| CRT platine dose ($mg/m^2$) | 25<br>40 | 7<br>51 | | 12.1%<br>87.9% | | 2<br>25 | | 7.4%<br>92.6% | 9<br>76 | 0.516 | $X^2$ |
| **NLR** | | | | | | | | | | | |
| Pretreatment | | 3.2 | ± | 1.9 | 2.7 | 3.8 | ± | 3.4 | 3.1 | 0.543 | m |
| Posttreatment | | 6.3 | ± | 6.1 | 4.3 | 6.5 | ± | 4.5 | 5.2 | 0.637 | m |
| Decresed NLR | | 10 | | 17.2% | | 6 | | 22.2% | 16 | 0.584 | $X^2$ |
| Incresed NLR | | 48 | | 82.8% | | 21 | | 77.8% | 69 | | |

ECOG-PS: Eastern Cooperative Oncology Group, performance score, NLR: Neutrophil-lymphocyte ratio, CRT: Chemoradiotherapy, RT: Radiotherapy, FIGO: International Federation of Gynecology and Obstetric, SD: Standard deviation, SCC: Squamous cell carcinoma

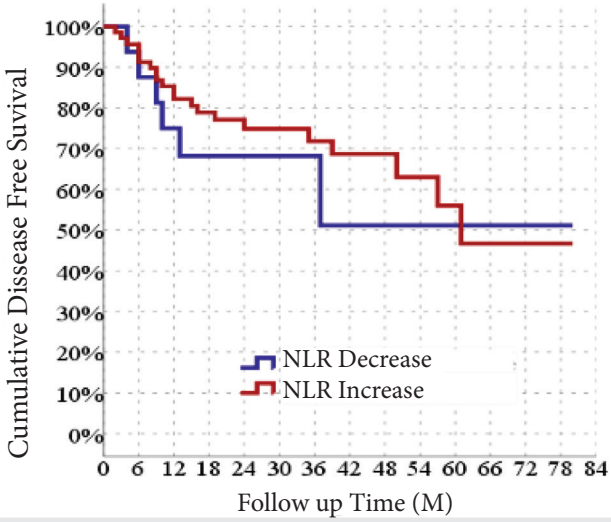



**Figure 1.** The relationship between NLR change with disease free survival
NLR: Neutrophil-lymphocyte ratio

### Study Limitations

First, this study is a retrospective investigation of a single institution, which is one of its limitations. Second, NLR may be affected by potential confounding variables. Third, our study's small sample size and demographic differences can limit how broadly our results can be applied; therefore further confirmation through a multicenter, extensive investigation is required.

## Conclusion

We did not observe a change in NLR values in the prognosis of patients treated with CRT. Enhancing comprehension of prognostic biomarkers like NLR, and the molecular mechanisms influencing their changes in cervical cancer patients receiving CRT may offer further clinical value to treatment decisions. However, it is crucial to understand their time dependency with regard to definitive therapy, as we continue to explore the usefulness of these markers.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-05-17, date: 18.03.2024).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Concept - E.D., M.Y.; Design - E.U.; Data Collection or Processing - R.Ç., İ.G., C.K.; Analysis or Interpretation - R.Ç., C.K.; Literature Search - R.Ç., E.D., S.Y.T.; Writing - R.Ç., İ.G.

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

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# Management, Prognosis and Early Mortality of Patients with Esophageal Perforation

Enver Reyhan[1], Habip Sarı[2], Hilmi Bozkurt[1], Kübra Şahin[1], Zekiye Nur Harput[3], Mehmet Kasım Aydın[3], Hakan Canbaz[1]

[1]Mersin University Faculty of Health Sciences, Department of General Surgery, Mersin, Türkiye
[2]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Gastroenterology Surgery, Ankara, Türkiye
[3]Mersin University Faculty of Health Sciences, Department of Gastroenterology, Mersin, Türkiye

## ABSTRACT

**Introduction:** The diagnosis, treatment, and follow-up of 19 patients diagnosed with esophageal perforation in our hospital were evaluated against the current literature.

**Methods:** The 19 patients diagnosed with esophageal perforation in our hospital's General Surgery Clinic between 2013 and 2023 were retrospectively examined in terms of demographic characteristics, perforation type, diagnostic method, time to treatment, localization and width of perforation, treatment methods applied, morbidity, and mortality.

**Results:** Of the 19 patients, 11 (57.9%) were male. The mean age was 59.2 (22-82). Etiologically, the most common cause was foreign body, and the most common level of perforation was the thoracic esophagus. Twelve of the patients were diagnosed within 24 hours. Six cases were managed non-operatively and followed with endoscopic intervention. 8 patients died.

**Conclusion:** Despite current diagnostic and therapeutic methods, esophageal perforation is still a disease with a high mortality rate.

**Keywords:** Esophageal perforation, mediastinitis, esophageal stent

## Introduction

Esophageal perforation is a rare condition, but when it does occur, it is associated with high morbidity and mortality. Mediastinitis due to a perforation may develop in patients, which is an extremely risky condition due to sepsis and mortality. The literature is unclear about the true incidence of esophageal perforation (1). With the widespread use of endoscopy for diagnosis and treatment, esophageal perforations have become more common (2). The symptoms and findings of esophageal perforation vary depending on the location of the perforation, how it happens, and the time since it was diagnosed. Apart from etiology and localization, Harrich et al. (3) classified esophageal perforations according to tomography and endoscopy findings.The perforations were all graded systematically from I to IV in the study according to the presence of air in the mediastinum, mediastinitis or sepsis, leakage of oral contrast, persistent fistula, long-stretch rupture or necrosis. Rapid diagnosis and treatment are vital, as the mortality rate almost doubles from 14% to 27% when diagnosed more than 24 hours after perforation (4). Treatment types include surgical methods such as open thoracotomy, thoracoscopy, or laparotomy and omentoplasty, as well as non-invasive methods such as endoscopic stenting (5). Another method to treat esophageal perforation is with endoscopic vacuum therapy, which is similar to negative pressure wound therapy (6). In this study, we aimed to evaluate and discuss the cause and location of perforation, along with the clinical features and treatment methods applied in 19 cases of esophageal perforation diagnosed and treated at our hospital, in light of the literature.

## Methods

The study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 1103, date: 13.11.2024), nineteen cases, for which data were available, diagnosed and treated with esophageal perforation in our hospital between 2013 and 2023 were retrospectively reviewed. Patient demographics, albumin, c-reactive protein, hemoglobin, platelet, creatinine values at the time of diagnosis, perforation type, diagnosis method, time to treatment, perforation location, and width, treatment methods, morbidity, and mortality were

**Address for Correspondence:** Kübra Şahin MD, Mersin University Faculty of Health Sciences, Department of General Surgery, Mersin, Türkiye
**E-mail:** kubr.sah@gmail.com **ORCID ID:** orcid.org/0000-0002-4085-6554

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analysed. Cases diagnosed within the first 24 hours were considered early diagnosis, and cases that were admitted to the hospital and diagnosed more than 24 hours later were considered late diagnosis.

### Statistical Analysis

The distribution of the study's data, which analyzed the cases of esophageal perforation, was evaluated by the Kolmogorov-Smirnov test. The data belonging to the cases were given as percentage, mean ± standard deviation, or median [minimum-maximum (max.)].

## Results

Eleven of the cases were male (57.9%) and eight were female (42.1%). The mean age was 59.2 (22-82). Table 1 shows the demographic characteristics, symptoms, radiological findings and primary pathology of the cases.

Seven of the cases (36.8%) were caused by foreign bodies, six cases (31.6%) were iatrogenic, with one occurring after thyroidectomy and five after endoscopy, and the (31.6%) were spontaneous perforations due to Boerhaave syndrome.

Twelve of the patients were admitted to the hospital within 24 hours and received an early diagnosis; seven patients were admitted and diagnosed after 24 hours. The diagnostic methods used in these cases were esophagoscopy or thoracic tomography.

Esophageal perforation occurred in two patients during the endoscopic dilatation procedure and in one patient during the procedure for variceal bleeding. One patient with esophageal cancer had a rupture during endoscopic stent placement. All of these patients were diagnosed at an early stage during the procedure.

Mediastinitis developed in 11 patients (57.9%), with one patient followed up for a neck abscess secondary to perforation. When evaluating the location of the perforation, seven patients (36.8%) had a perforation in the thoracic oesophagus. Six (31.6%) patients had a perforation at the level of the cervical esophagus, and six (31.6%) the abdominal esophagus. The max perforation width was determined to be 7 cm.

Diagnostic chest tomography revealed pneumomediastinum in 13 patients (68.4%), bilateral pleural effusion in five patients, and left-sided pleural effusion in one patient. In addition, pneumothorax was noted in two patients.

Surgery was used as a treatment in 13 patients (68.4%). In nine of these cases, the perforation site was accessed through thoracotomy, while in four, a cervical incision was used. In one case, a feeding gastrostomy was performed in the same session through a median incision above the umbilicus. In three cases, the distal esophagus was closed, in two of them a drain was placed from the proximal esophagus to the hypopharynx to provide drainage, and in one of them a cervical esophagostomy procedure was performed Two patients had an esophagectomy, and three a primary suture of the perforation. Anastomotic leakage developed in one patient, and anastomotic repair was performed by relaparotomy. As a postoperative complication, a tracheopleural fistula developed in one patient. Dehiscence of the wound also occurred in one patient, who underwent a revision of the wound. Total parenteral nutrition (TPN) support therapy was provided in all cases. Intraoperative endoscopy was performed in four patients; three of them underwent intraoperative endoscopic stenting, while the other patient underwent hemoclip placement. Six cases were followed non-operatively with endoscopic intervention. Stents were placed in 3 of these patients and hemoclips were applied to the other 3. The mean hospital stay was 19 (1-80) days.

Eight patients (42.1%) died. Four of these were in the group of patients diagnosed early.One patient in this group, who was diagnosed early and died, is included in the group of patients managed non-operatively with endoscopic intervention.

**Table 1. The demographic characteristics, symptoms, radiological findings and primary pathology of the cases**

| | |
|---|---|
| **Age (year)** | 59.2±29.9 |
| **Gender (%)** | |
| Male | 11 (57.9%) |
| Female | 8 (42.1%) |
| **Symptoms and signs (%)** | |
| Neck abscess | 1 (5.3%) |
| Chest pain | 3 (15.8%) |
| Dyspnea | 9 (47.4%) |
| Dysphagia | 6 (31.6%) |
| **Etiology (%)** | |
| Foreign body | 7 (36.8%) |
| Iatrogenic | 6 (31.6%) |
| Spontaneous | 6 (31.6%) |
| Mediastinitis (%) | 11 (57.9%) |
| **Perforation level (%)** | |
| Cervical | 6 (31.6%) |
| Thoracic | 7 (36.8%) |
| Abdominal | 6 (31.6%) |
| **Pneumomediastinum(%)** | 13 (68.4%) |
| **Pleural effusion** | 5 (26.3%) |
| **Need for surgery** | 13 (68.4%) |
| **Duration of hospitalisation (day)*** | 19 (1-80) |
| **Mortality** | 8 (42.1%) |
| **Diagnostic time (%)** | |
| Early | 12 (63.2%) |
| Late | 7 (36.8%) |
| CRP (mg/L)* | 52 (0.1-511) |
| **Hemoglobin level (g/dL)** | 12.4±2.4 |
| White blood cells (x$10^3$/µL)* | 12745 (4386-115000) |
| Platelets (x$10^3$/µL) | 277166±113011 |
| Creatinine (mg/dL) * | 0.69(0.21-2.08) |
| Albumin (gr/dL) | 3.2±0.67 |

*Signed data are given as median (minimum-maximum) because they are not normally distributed
CRP: C-reactive protein

## Discussion

This study was conducted through a retrospective evaluation of 19 esophageal perforations diagnosed and treated in our clinic.

Esophageal perforation is a rare condition, but when it does occur it is associated with high morbidity and mortality. Due to the effectiveness of many specialties such as cardiology, general surgery, thoracic surgery and gastroenterology in the diagnosis and treatment of esophageal diseases, there is an increase in the use of endoscopic diagnostic and treatment methods in esophageal pathologies. Therefore, whereas spontaneous injury used to be the most common etiology of esophageal perforation, today more than half of all esophageal perforations are iatrogenic, and most of them occur during endoscopy (7). Especially when an intervention such as therapeutic dilatation is added to upper gastrointestinal endoscopy, the probability of perforation reaches 0.1% (4,8). for this reason, when a balloon dilation procedure is performed in achalasia, even the slightest suspicion of a perforation should be monitored. One of our cases was diagnosed with achalasia and perforated following endoscopic dilatation. In this case, the esophageal perforation was treated surgically. Esophageal perforation was the result of an endoscopic procedure in five of our cases, two of which were caused by endoscopic dilatation. The localizations where esophageal perforations are seen in the literature are in order of frequency, cervical, abdominal, and thoracic (6%, 21%, 27%) (9). In our study, consistent with the literature, the most common localization of esophageal perforation was the thoracic region. Spontaneous esophageal perforations usually occur at the distal supracardiac level. In our cases, spontaneous rupture was the cause of two of the five patients who developed a perforation at the level of the abdominal esophageal tract. Esophageal perforation after foreign body ingestion accounts for approximately 12% of the etiology, and is common at the level of the cricopharyngeus muscle. Esophageal perforation after foreign body ingestion accounts for approximately 12% of the etiology and often occurs at the level of the cricopharyngeal muscle (10). The most common cause in our cases was a foreign body, with seven cases. In three of the patients who developed perforation at the level of the cervical esophagus, the cause was a foreign body. Perforation may also occur after surgical procedures such as vertebral surgery, thyroidectomy, decortication, mediastinal lymph node dissection, and tracheotomy (1,2). In a case diagnosed with anaplastic thyroid cancer, esophageal perforation, along with associated esophageal fistula and neck abscess, developed after thyroidectomy.

The dominant radiological finding seen in our cases was pneumomediastinum. Perforations in the distal part of the esophagus cause pneumothorax on the left, while those more proximally, cause pneumothorax on the right (5,11). Two of our cases had pneumothorax on the left. In both cases, the perforation was at the distal esophageal level. Furthermore, if the esophageal tract is perforated, mediastinitis and pleural inflammation may develop within a short time.The development of sepsis and mortality is extremely common in these patients. Eleven of our cases developed mediastinitis. Our mortality rate was 42.1%.

There are two approaches in the treatment of esophageal perforation: conservative and surgical. Non-surgical treatment of esophageal perforation can be applied in stable patients with early onset, limited esophageal mucosal disruption, and minimal contamination of surrounding spaces (12). Conservative management includes stabilising the patient within 48 hours of injury, TPN, and broad-spectrum antibiotic therapy for at least 7 days (2). Endoscopy has a significant place in the non-invasive treatment of esophageal perforation. Many esophageal perforations that are related to endoscopy can also be treated endoscopically (13,14). Nowadays, it is possible to achieve mechanical closure of an esophageal perforation with endoscopic clips. Endoscopic procedures can also be performed using tissue adhesives or stents (15). Six patients were treated non-invasively, three underwent endoscopic stent placement, and three underwent endoscopic hemoclip placement. One patient undergoing non-invasive treatment resulted in death. Primary repair, resection, separation, and esophagostomy are the most common methods of surgical treatment. In our cases, surgical treatment was applied to 13 patients, primary repair was performed in three patients, resection in two patients, and esophagectomy and esophagostomy in three patients, within a total of 13 patients who received surgical treatment.

Intraoperative endoscopic intervention is also one of the possible treatment methods (16,17). The most important factor in survival in esophageal perforation is early diagnosis and early treatment intervention (18). With early diagnosis and surgery, survival has been reported to be 93% (12). Sepsis causes multiple organ failure and is a leading cause of death (19). Nowadays, there is a shift away from aggressive treatments such as esophagectomy and esophagostomy, with less aggressive methods becoming more common (20). With the development of endoscopic procedures in recent years, it is now possible to perform effective non-invasive treatment of esophageal perforations. Intraoperative endoscopic treatment was performed in four patients. Mortality occurred in two of 10 patients who received endoscopic intervention and in seven of 12 patients who had surgery.

### Study Limitations

The limitations of our study were that it was retrospective, and the number of patients was small due to it being a single-centre study.

## Conclusion

Despite today's improvements in examination and treatment, esophageal perforation is still a serious health problem. Despite better outcomes with early diagnosis of non-abdominal esophageal perforation and endoscopic intervention that occurs especially in the first 24 hours, esophageal perforation remains an important cause of mortality.

### Ethics

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethics Committee of Mersin University (approval number: 1103, date: 13.11.2024).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Surgical and Medical Practices - E.R., H.B., H.C.; Concept - E.R., H.S., H.B., K.Ş.; Design - E.R., H.S., H.B., K.Ş.; Data

Collection or Processing - H.S., H.B., K.Ş., Z.N.H., M.K.A.; Analysis or Interpretation – E.R., H.S., H.B.; Literature Search - E.R., H.B., K.Ş., H.C.; Writing – E.R., H.B., K.Ş.

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# Effectiveness of Venom Immunotherapy: A Single-center Experience

Fatma Arzu Akkuş[1], Fatih Çölkesen[1], Tuğba Önalan[1], Recep Evcen[2], Mehmet Kılınç[3], Filiz Sadi Aykan[4], Mehmet Emin Gerek[1], Şevket Arslan[1]

[1]Necmettin Erbakan University Faculty of Health Sciences, Department of Clinical Immunology and Allergy, Konya, Türkiye
[2]Recep Tayyip Erdoğan University Faculty of Health Sciences, Department of Immunology and Allergy, Rize, Türkiye
[3]Batman Training and Research Hospital, Clinic of Immunology and Allergy, Batman, Türkiye
[4]University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Immunology and Allergy, Ankara, Türkiye

## ABSTRACT

**Introduction:** Treatment outcomes in patients who completed or suddenly discontinued venom immunotherapy (VIT) are still uncertain.

**Methods:** A total of 71 patients who received conventional VIT were included in the study. Patients who experienced field stings were invited to the clinic, and allergic reactions were evaluated.

**Results:** The median age of the patients was 43 (35-54) years, and 70.4% (n=50) were male. Of the patients, 32 (45.1%), 29 (40.8%), and 10 (14.1%) received VIT with Vespula venom, Apis venom, and both Vespula and Apis venoms, respectively. Treatment was interrupted in 57 (80.2%) patients who could not access VIT due to drug unavailability. Thirty-eight (53.5%) patients experienced resting after initiation of VIT. Of the re-stung patients, 22 (57.8%) developed local reactions (LRs), and 16 (42.1%) developed systemic allergic reactions (SARs). All four patients who experienced anaphylaxis after re-sting were those whose treatment of VIT was incomplete. The VIT duration of patients with SARs was shorter than that of patients with LRs, although not significantly. SAR after the sting was significantly lower in patients with VIT duration >4 years. Thirty-three (46.5%) patients reported carrying adrenaline auto-injectors (AAIs), and 8 of them self-administered an AAI.

**Conclusion:** The effectiveness of VIT was correlated with its duration, and VIT lasting at least four years prevents SARs after field stings. The proportion of AAI carriers and the rate of self-administration were low among patients on VIT.

**Keywords:** Allergy, adrenaline auto-injector, hymenoptera venom, field sting, systemic allergic reaction, venom immunotherapy

## Introduction

Stings by the order Hymenoptera, are common. Approximately 56.6%-94.5% of the general population is stung at least once during their lifetime (1). Bees from the Apidae and Vespidae families belong to this order. *Apis mellifera* (honeybee) of the Apidae family and *Vespula* spp. (wasp, yellow jacket) of the Vespidae family frequently cause allergic reactions (2). After a sting, Hymenoptera venom allergy (HVA) may be life-threatening (3). The onset of HVA cannot be predicted. A systemic allergic reaction (SAR) can occur after subsequent stings, even in those who did not experience a SAR during previous encounters (1). Sting symptoms vary from local reactions (LRs) at the sting site to SARs (4). Patients with HVA have a poor quality of life because even the course of mild systemic reactions cannot be predicted (2).

The incidence of anaphylaxis in sting-induced SAR is 0.6-42.8% (5). HVA ranks among the top three causes of anaphylaxis (6). The rate of recurrence of SAR following a subsequent sting in adults is 20%-70% (7). Hymenoptera venom-induced anaphylactic reaction is a clinical emergency. The patient must recognize this emergency and be informed regarding its acute management (8). The major treatment for Hymenoptera sting-induced anaphylaxis is intramuscular epinephrine. Delayed administration of epinephrine is a risk factor that may determine an unfavorable outcome of the acute anaphylactic episode. For patients with SAR, the teaching of appropriate techniques for self-administration of adrenaline and the prescription of an adrenaline auto-injector (AAI) are necessary to prevent future anaphylaxis (6).

The only protective treatment for systemic reaction following Hymenoptera sting is venom immunotherapy (VIT). VIT is indicated for patients who are determined to have a history of sting-induced systemic reaction and to have sensitivity to venom of the liable insect by skin prick testing responses and/or serum specific IgE (sIgE) tests and/or basophil

**Address for Correspondence:** Fatma Arzu Akkuş MD, Necmettin Erbakan University Faculty of Health Sciences, Department of Clinical Immunology and Allergy, Konya, Türkiye
**E-mail:** arzusmr@hotmail.com **ORCID ID:** orcid.org/0000-0003-0519-7132

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activation tests When the first sting reaction is severe and allergy testing is similarly positive for *Vespula* and *Apis* venoms, VIT using both venoms should be considered (4). VIT provides protection against SAR in 77%-84% of honeybee stings and 91%-96% of vespid stings (5). Following discontinuation of the treatment, a long-term effect is observed. There is no biomarker of the response to allergen immunotherapy to aid decision-making regarding VIT continuation or discontinuation (9). Life-long treatment should be considered in patients who experience SARs or systemic side effects during VIT, and in patients with honeybee venom allergy and a high risk of future honeybee stings (4).

Allergen immunotherapy can alter the natural course of allergic diseases by reducing medication use and providing long-lasting symptomatic control. Indeed, it is the only potentially curative treatment (9). It not only ameliorates the disease by reducing the number of reactions, but also improves the psychological quality of life (10). Some of the patients started on VIT could not complete their treatment due to drug supply disruptions in Türkiye. We retrospectively analyzed the sting reactions of all patients during and after VIT, as well as the proportion of AAI carriers among these patients.

## Methods

### Study Design

The study was approved by the Non-Drug and Medical Device Research Ethics Committee of Necmettin Erbakan University (approval number: 2024/4852, date: 15.03.2024). A total of 83 patients who received VIT in the Adult Immunology and Allergy Department between January 2016 and April 2022 were reviewed. The demographic characteristics, clinical histories, and laboratory results of the patients were retrieved from their medical records and electronic health records. All patients who had initiated VIT at the hospital were contacted by phone; 12 patients who could not be reached were excluded from the study. Patients who did not complete their treatment were invited for a follow-up visit. Informed written consent were obtained from all participants.

### Venom Immunotherapy

VIT was initiated using Alutard SQ allergen extract (ALK-Abelló, Denmark) for patients with honeybee and wasp venom allergy. Doses were administered under physician supervision in an equipped treatment room. The injections were performed according to the conventional protocol with weekly increasing doses and a 15-week up-dosing scheme. During the maintenance phase, which was reached within about 16 weeks, the interval between the injections was gradually increased. The standard maximal maintenance dose of 100,000 U-SQ/mL was reached. Maintenance treatment was planned to last >5 years in all patients. Patients with VIT ≥5 years were considered to have completed treatment. However, due to the poor availability of immunotherapy in Türkiye for the last 2 years, VIT was discontinued in patients.

### Venom-Specific IgE Antibodies

Allergy was diagnosed based on a conclusive history and a corresponding venom sensitization (sIgE) in serum. Before beginning VIT, basal serum tryptase (sBT) and sIgE antibodies against *Apis* and *Vespula* venoms were assayed. The plasma sIgE titers were measured using the Phadia Unicap 100 instrument (Thermo Fisher Scientific, Waltham, MA) and the Immuno-CAP system by fluoroenzyme immunoassay. The results are expressed as kilounits per liter. An *Apis* and/or *Vespula* sIgE level of ≥ 0.35 kU/L was considered indicative of positivity.

### Severity of Reactions

Patients experiencing stings were in the maintenance phase. Allergic reactions following re-sting were graded by severity. A mild SAR was defined as cutaneous symptoms including itching, urticaria, erythema, and mild angioedema. A moderate SAR was defined as transient symptoms of hypotension, dyspnea, abdominal pain, vomiting, dizziness, and vertigo. A severe SAR was defined as anaphylaxis, hypotension, loss of consciousness, and asthma-induced and laryngeal edema-induced dyspnea (11).

### Statistical Analysis

Data entry and statistical analysis were performed using the SPSS statistical package (v. 22.0; SPSS Inc. Chicago, IL). Continuous variables are expressed as medians and interquartile ranges, and categorical variables as numbers and percentages. Comparison of non-normally distributed numerical data with categorical data was performed using the Mann-Whitney U test. For comparison of categorical data, Pearson's chi-squared test and Fisher's exact test were used. A value of $p<0.05$ was considered indicative of statistical significance.

## Results

### Demographic and Clinical Characteristics

Seventy-one patients who had SARs following a Hymenoptera sting, confirmed sensitivity, and who received VIT, were included in the study. sIgE against the responsible insect confirmed the patients' venom allergy. The median age of the patients was 43 (35-54) years, and 50 (70.4%) were male. All 11 beekeepers (15.5%) were male. Of the patients, 29 (40.8%) received VIT using *Apis* venom and 32 (45.1%) received VIT using *Vespula* venom, respectively. Ten patients (14.1%) reported allergic reactions after both *Apis* and *Vespula* stings. These patients, who were found to be sensitized to both venoms, received VIT using both venoms. Patients received VIT for an average of 42 (9-53) months. Of the patients, 14 (19.7%) completed VIT (VIT ≥5 years); 57 (80.2%) did not complete 5 years of VIT because of the poor availability of VIT in Türkiye (Table 1).

### Reactions due to Accidental Field Re-Stings

After initiation of VIT, 38 (53.5%) patients experienced stings. Of the 38 patients who experienced stings, only 8 received VIT for ≥5 years, while 30 were patients who had discontinued VIT. Among them, 18 (47.3%) experienced field stings during VIT, and 20 (52.6%) after VIT was discontinued (Figure 1). Of the patients, 21 and 17 reported *Apis* and *Vespula* re-stings, respectively. Two patients re-stung by a bee other than the one for which VIT was administered, developed LRs. Of the re-stung patients, 22 (57.8%) developed LRs and 16 (42.1%) developed SARs. The four patients who developed severe SARs had symptoms of anaphylaxis (Table 2).

**Table 1. Demographic, clinical and immunotherapy parameters**

| Variables | | Data |
|---|---|---|
| Total number of patients | | 71 |
| Age (median-IQR) | | 43.0 (35.0-54.0) |
| Gender, n (%) | Female | 21 (29.6) |
| | Male | 50 (70.4) |
| Venom immunotherapy, n (%) | Apis VIT | 29 (40.8) |
| | Vespula VIT | 32 (45.1) |
| | Double VIT | 10 (14.1) |
| Occupation, n (%) | Beekeeping | 11 (15.5) |
| | Others | 60 (84.5) |
| Duration of VIT, month (median-IQR) | | 42.0 (8.0-53.0) |
| Duration of VIT, n (%) | <1 year<br>1 to 3 years<br>>3 years<br>Completed VIT | 20 (28.2)<br>14 (19.7)<br>23 (32.4)<br>14 (19.7) |

VIT: Venom immunotherapy, IQR: Interquartile range

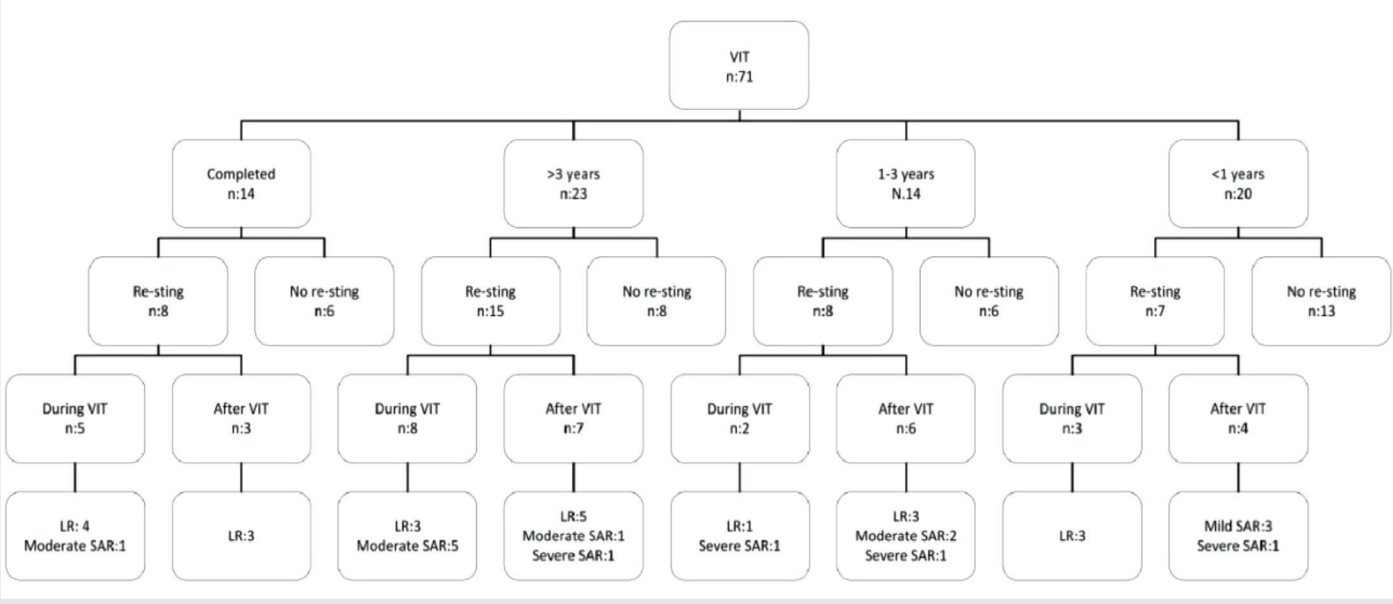



**Figure 1.** Patients reacting to field re-sting during or after VIT by duration of VIT
VIT: Venom immunotherapy, LR: Local reaction, SAR: Systemic allergic reaction

Of the re-stung patients with a VIT duration <1 year, three developed LRs and four developed SARs, of which three were mild and one was anaphylaxis. Of the re-stung patients with a VIT duration of 1-3 years, four developed LRs and four developed SARs (two moderate and two cases of anaphylaxis). Of the re-stung patients with a VIT duration >3 years, eight developed LRs and seven developed SARs, six moderate and one anaphylaxis. Of the re-stung patients who completed VIT, seven developed LRs and one developed moderate SARs. Figure 1 shows, in detail, the timing of patient stings and their reactions in relation to the duration of VIT.

### Competence with the AAI

Of the patients, 33 (46.5%) reported that they carried AAIs, and 38 (53.5%) reported that they did not. In addition, 20 of 38 re-sting patients had AAI. Of the 20 patients carrying AAI who were re-stung, 8 self-administered AAI, while 12 did not. Six of the eight patients who self-administered AAIs were admitted to an emergency department (ED) (Table 2). Of the patients who self-administered AAIs, three did so before symptom onset and five had SAR symptoms. Three of the five patients who had SARs and self-administered AAIs developed anaphylaxis. Four patients with anaphylaxis were admitted to an ED, three of whom self-administered AAIs. Six of eleven beekeepers carried AAIs.

### Comparison of Types of Reaction Observed in Bee-Stung Patients and Their Demographic and Immunotherapy Characteristics

The median age of patients who experienced SARs after re-sting was 42 years, compared to 51.5 years for those who experienced LRs (p=0.042). The gender distribution, occupations, and AAI self-administration

status were similar between the patients who experienced SARs and LRs (p>0.05). The median time of administration was 39 months and 50 months in patients with SARs and LRs, respectively (p=0.052). The type of reaction did not differ between patients with VIT durations of >3 years and ≤3 years (p=0.258). However, the type of reaction differed between patients with VIT duration of >4 years and ≤4 years (p=0.037) of 11 beekeepers, 10 were re-stung (Table 3).

## Discussion

VIT is the only curative modality for HVA. It requires injections every 4-8 weeks and must be continued for 3-5 years, making it costly. We evaluated reactions after field re-sting in patients who started but did not complete VIT due to the unavailability of VIT in Türkiye and in patients who received VIT for ≥5 years in Türkiye. Of the 71 patients receiving VIT, 38 experienced accidental field re-sting during or after VIT. Among them, 16 reported SARs. The VIT duration of the patients

**Table 2. Identified insects and results of field stings**

| Variables | | Data |
|---|---|---|
| Field re-sting, n (%) | Yes<br>No | 38 (53.5)<br>33 (46.5) |
| Stinging bee species | Apis<br>Vespula | 21<br>17 |
| Number of field stings, n | Without allergic reactions<br>With allergic reactions<br>Mild SAR<br>Moderate SAR<br>Severe SAR | 22<br>16<br>4<br>8<br>4 |
| Carrying AAI, n(%) | Yes<br>No | 33 (46.5)<br>38 (53.5) |
| Carrying of AAI, n | Yes<br>Using AAI<br>AAI alone<br>AAI + hospital visit<br>Not using AAI<br>Hospital visit<br>No | 33<br>8<br>2<br>6<br>12<br>6<br>38 |

SAR: Systemic allergic reaction, AAI: Adrenaline auto-injector

**Table 3. Comparison of types of reactions in patients re-stung after immunotherapy and their demographic, clinical and immunotherapy characteristics**

| Characteristics<br>SAR (n=16) | | Patients re-stung after initiation of immunotherapy (n=38) | | p |
|---|---|---|---|---|
| | | LR (n=22) | | |
| Age (median-IQR) | | 42.0 (30.7-52.7) | 51.5 (38.5-58.0) | **0.042**[a] |
| Gender, n (%) | Female | 6 (37.5) | 4 (18.2) | 0.168[b] |
| | Male | 10 (62.5) | 18 (81.8) | |
| Occupation, n (%) | Beekeeping | 5 (31.3) | 5 (22.7) | 0.411[b] |
| | Others | 11 (68.8) | 17 (77.3) | |
| VIT, n (%) | Apis | 8 (50.0) | 10 (45.5) | - |
| | Vespula | 5 (31.3) | 9 (40.9) | |
| | Double VIT | 3 (18.8) | 3 (13.6) | |
| Using AAI, n (%) | Yes | 5 (31.3) | 3 (13.6) | 0.181[b] |
| | No | 11 (68.8) | 19 (86.4) | |
| Duration of VIT, month (median-IQR) | | 39.0 (9.7-47.2) | 50.0 (36.0-60.0) | 0.052[a] |
| Duration of VIT n (%) | ≤3 years | 8 (50.0) | 7 (31.8) | 0.258[c] |
| | >3 years | 8 (50.0) | 15 (68.2) | |
| Duration of VIT n( %) | ≤4 years | 12 (75,0) | 9 (40,9) | **0.037**[c] |
| | >4 years | 4 (25.0) | 13 (59.1) | |

[a]: Mann-Whitney U test; [b]: Fisher's exact test; [c]: Pearson's chi-squared test
VIT: Venom immunotherapy, LR: Local reaction, SAR: Systemic allergic reaction, IQR: Interquartile range

who experienced SAR was shorter than that of those who experienced LRs, although not significantly. SAR after sting was also lower in patients with VIT duration >4 years (p=0.037). Thus, >4 years of VIT protected patients from SAR. All four patients with severe SAR who reported symptoms of anaphylaxis had their VIT discontinued. Of the patients who completed VIT, seven developed LRs and one developed SARs, after re-sting. The awareness of patients receiving VIT of carrying and self-administering AAI was poor; only 33 of the patients receiving VIT, were carrying an AAI. Among the 20 re-stung patients carrying an AAI, only 8 self-administered AAI.

In a previous study in Türkiye, 29% of the general population was sensitized to Hymenoptera venom. Hymenoptera stings and allergies are typically caused by honey bees (*A. mellifera*) and wasps (*Vespula* vulgaris) (12). In this study, rates of VIT using *Apis* (40.8%) and *Vespula* (45.1%) venom were similar. Component-resolved testing was not available in our clinic to eliminate cross-reactivity in patients susceptible to both venoms. Among the patients with sensitization to both venoms, 10 patients (14.1%) with a history of reaction to both *Apis* and *Vespula* stings underwent VIT with both venoms. When the causative insect was identified, we administered VIT using only the causative species, even in the presence of determined sensitivity to both bee species.

The incidence of allergy to Hymenoptera stings is higher among males (13). In our study, 50 (70.4%) of the patients receiving VIT were male. Field re-sting was more common in male patients than in female patients (28/10). The increased risk of re-sting, might be because of the larger number of male patients than female patients. In this study, 11 beekeepers (15.5%) were males. All 11 beekeepers received VIT using *Apis* venom; 10 experienced re-stings. The rate of SAR after re-stings among beekeepers is reportedly 14%-38%, which is higher than in the general population (14). In this study, among 10 re-stung beekeepers, 4 had LRs, 2 had mild SARs, and 1 had a severe SAR.

SARs following accidental Hymenoptera stings have been reported, even in individuals with negative sensitivity tests after VIT (15). Evaluating the effectiveness of VIT is thus challenging. A sting challenge test, involving an insect to which a patient is allergic to sting, is the gold standard for demonstrating the effectiveness of VIT (4). When this test cannot be performed, the results of natural field sting reactions may be beneficial for evaluating the effectiveness of VIT. While accidental field stings were recorded in some studies, intentional sting challenges were recorded in hospital settings in others (15). In this study, 38 patients (53.5%) experienced re-sting after initiation of VIT. The likelihood of field sting was similar to previous reports (50% to 62%) (16,17).

The risk of SAR after re-sting is higher in individuals with *Apis* venom allergy (18). Furthermore, the effectiveness of VIT for *Apis* venom is lower than for *Vespula* venom. The rate of recurrence after discontinuation of VIT is 7.5% for *Vespula* and 15.8% for *Apis* (19). In this study, 62.5% of SARs involved *Apis* after accidental field re-sting, possibly because 55% of the re-stung patients (21/38) reported re-stings with *Apis*, or because A. mellifera injects a large quantity of venom (5). Similarly, we observed that re-sting reactions to *Apis* were more dangerous than those to *Vespula*.

HVA-induced anaphylaxis is associated with increased sBT and mastocytosis in 5% of cases (20). However, we found neither increased sBT levels nor mastocytosis in our patients. Thus, mastocytosis, a factor known to cause VIT treatment failure, was not found in this study.

The rate of SAR after re-sting was 60% in untreated patients, while it was 5% in those on VIT. The rate of recurrence of SAR after discontinuation of VIT is 10%-15% higher in patients treated for <5 years (21). In this study, 16 of 38 patients who experienced field re-stings (42%) developed SARs. The high rate of SARs is likely attributed to not all the patients having received VIT for a sufficient duration, which is a determinant of its long-term effectiveness. In this study, the VIT duration was not significantly different among patients who developed LRs after field re-sting compared to those who experienced SARs. SARs occurred in 8 of 15 re-stung patients who had received VIT for ≤3 years, and 3 of the 8 SARs were anaphylaxis. Immunotherapy was highly effective in a previous study, with a 3% incidence of sting-related reactions after four years of VIT (22). In this study, among re-stung patients, SAR developed more significantly in those with VIT <4 years. None of the re-stung patients who completed VIT developed anaphylaxis. Because of the residual risk of SAR, patients are advised to take precautions against Hymenoptera stings and to carry AAIs, including those on VIT (23).

AAIs are infrequently used by patients of all ages to treat anaphylaxis (24). In a Japanese study, 30%-50% of outdoor workers and 30% of beekeepers with a history of SARs after Hymenoptera stings were carrying AAIs (25). In this study, 33 (47%) of the patients were carrying AAIs. Of 11 beekeepers, 6 (55%) were carrying AAIs. The most common reason for not carrying AAIs was that they had expired and were not prescribed again. Another reason was the inconvenience of carrying AAIs, resulting from their large size. Among individuals with a history of anaphylaxis, the rate of self-administration of AAI was 27% (26). In this study, 8 of 20 re-stung patients (40%) who were carrying AAIs self-administered AAIs. The most common cause of non-use of AAI was confusion about its timing. The mortality rate increases if adrenaline injection is delayed by more than 30 minutes after the occurrence of an SAR following a Hymenoptera sting. Appropriate use of AAI is important (25).

**Study Limitations**

One limitation of the study is the small patient population. Therefore, the results are not fully generalizable. Another issue is the large number of patients who failed to complete treatment due to the abrupt discontinuation of VIT supply in Türkiye. Thus, evaluating the effectiveness of VIT became complicated because the duration of VIT was extremely variable among the patients. Since the supply of VIT has not been established in our country, treatment has not yet been restarted for patients with incomplete therapy. Another limitation of this study is that we were unable to study biomarkers of susceptibility other than sIgE (e.g., component-based testing) and therefore could not include these parameters in our analysis. We also believe that a detailed evaluation of clinical symptoms, is crucial for the diagnosis and differentiation of HVA.

## Conclusion

Our objective in this study was to determine the reactions after accidental field stings in the patients receiving VIT, particularly in patients whose treatment was aborted due to poor availability of VIT in Türkiye. The incidence of SAR after field re-sting was higher in patients whose VIT was discontinued. The patients who experienced anaphylaxis after re-sting failed to complete VIT or received VIT for a short period. Our results strongly suggest that the effectiveness of VIT mainly depends on the duration of treatment. In patients who discontinue VIT after 3 to 4 years, it would be useful to prospectively evaluate recurrent systemic sting reactions with sting challenge test. Another important aspect of this study is the demonstration of lower rates of carrying and self-administration of AAI among patients receiving VIT. The fact that some patients experienced anaphylaxis after re-sting despite being on VIT suggests the importance of carrying an AAI.

### Ethics

**Ethics Committee Approval:** The study was approved by the Non-Drug and Medical Device Research Ethics Committee of Necmettin Erbakan University (approval number: 2024/4852, date: 15.03.2024).

**Informed Consent:** Informed written consent were obtained from all participants.

### Footnotes

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

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

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# Umbilical Trochar Site is the Usual Suspect for Trocar Site Hernia After Laparoscopic Cholecystectomy: A Prospective Study

Tolga Canbak[1], Olgun Erdem[2], Mehmet Erman Bacaksız[1], Aylin Acar[1], Fatih Başak[1]

[1]University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, Clinic of General Surgery, İstanbul, Türkiye
[2]Bingol State Hospital, Clinic of General Surgery, Bingöl, Türkiye

## ABSTRACT

**Introduction:** Trocar site hernia (TSH) is a rare but clinically significant complication of laparoscopic cholecystectomy (LC). This study aimed to evaluate the association between gallbladder retrieval site selection and postoperative TSH incidence.

**Methods:** In this prospective, randomized study, 110 patients undergoing LC were allocated to either the umbilical (n=55) or epigastric (n=55) gallbladder retrieval groups. Surgical techniques and postoperative management were standardized. Patients were followed for one year, with routine ultrasonography performed at 6 and 12 months regardless of symptoms. The primary outcome was the level of TSH. Secondary outcomes included postoperative pain and retrieval time.

**Results:** Fifty patients in each group were included in the final analysis. TSH occurred in 6 patients (12%) in the umbilical group and 5 patients (10%) in the epigastric group (p=1.00), with all hernias located at the umbilical site for both groups. Gallbladder retrieval time was significantly shorter in the epigastric group (p=0.013), whereas the umbilical retrieval was associated with significantly lower pain at 6 hours postoperatively (p=0.027). Multivariate analysis identified extraction site widening as the only independent risk factor for TSH (odds ratio =4.08, p=0.05).

**Conclusion:** The site of extraction did not significantly influence TSH rates, which consistently occurred at the umbilical site. Epigastric extraction shortened retrieval time but was associated with slightly higher early postoperative pain. Standardizing the technique and minimizing fascial dilation appear critical for reducing the risk of TSH. Future studies should explore the role of a 5-mm umbilical trocar to further mitigate hernia development.

**Keywords:** Trocar site hernia, incisional hernia, port site hernia, laparoscopic cholecystectomy

## Introduction

Laparoscopic cholecystectomy (LC) is one of the most commonly performed surgeries worldwide and remains the most frequent laparoscopic procedure. It is primarily indicated for gallstones, gallstone pancreatitis, acute cholecystitis, and gallbladder polyps (1). Although LC is considered a minimally invasive technique, it is not without complications-some of which can be severe or even fatal (2).

Trocar site hernia (TSH), a herniation occurring at a trocar site after laparoscopic surgery, is a relatively rare but significant postoperative complication. Despite its low incidence, TSH can markedly increase patient morbidity by necessitating reoperation, increasing readmissions and costs, and ultimately diminishing the benefits of minimally invasive surgery. Reported TSH incidence rates vary widely, ranging from 1% to 25% (3-5). Clinically, TSH may present as a palpable lump, pain, skin discoloration, or thinning at the trocar site. In some cases, it may remain asymptomatic until complications such as incarceration occur (6).

To mitigate the risk of TSH, various preventive strategies have been proposed. Routine closure of fascial defects larger than 10 mm is a standard practice (7). Additionally, the use of bladeless trocars and smaller-diameter trocars (e.g., 5 mm) has been associated with a reduced TSH risk (8,9).

**Address for Correspondence:** Olgun Erdem MD, Bingol State Hospital, Clinic of General Surgery, Bingöl, Türkiye
**E-mail:** olgun.erdem@hotmail.com **ORCID ID:** orcid.org/0000-0003-1433-3431

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Several risk factors for TSH have been well documented. Among them, the organ extraction phase of the surgery may exert additional mechanical stress on the trocar site, potentially enlarging fascial defects and increasing the likelihood of hernia formation (10).

Previous studies examining risk factors for TSH have largely been retrospective, with inconsistent follow-up and limited focus on the choice of extraction trocar site. In this study, we conducted a prospective cohort analysis to evaluate the association between TSH and the location of the organ extraction trocar. By controlling for known confounders, comparing umbilical and epigastric extraction sites, and incorporating extended follow-up, we aimed to provide more robust and clinically relevant evidence regarding this underexplored factor.

## Methods

### Study Ethics

The study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, Clinical Research Ethics Committee (approval number: 106, date: 31.03.2022), and the study was registered with ClinicalTrials.gov (Study Id: NCT06953713). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for participation in and publication of the study. This study was conducted and reported in accordance with the CONSORT guidelines.

### Study Design

One hundred and ten patients were enrolled in this two-arm study (n=55 per group). A power analysis was conducted to determine the required sample size for detecting a difference in incisional hernia rates between the two groups (umbilical vs. epigastric retrieval). Assuming a two-sided alpha level of 0.05 and a power of 80%, a minimum (min) of 47 patients per group was required to detect a statistically significant difference. To account for potential dropouts or loss to follow-up, we enrolled 55 patients in each group. The sample size calculation was performed using G*Power 3.1 software (Heinrich Heine University, Düsseldorf, Germany).

Patients were blinded to group allocation. Randomization was performed on the day of surgery by a surgical nurse using the Alea Randomisation mobile application (Alea Clinical Services, Abcoude, Netherlands). A sealed envelope containing the allocation (“U” or “E”) was delivered to the operating room and opened by the attending surgeon prior to specimen retrieval. Due to the nature of the intervention, the operating surgeon was not blinded; however, they were unaware of group assignment until the point of retrieval. All surgeries were performed by the same three experienced surgeons.

Routine antibiotic prophylaxis was administered with 2 g of intravenous cefazolin (Sefazol, Gensenta İlaç, İstanbul, Türkiye).

A standard four-trocar LC was performed using a 10-mm umbilical camera trocar, a 10-mm epigastric trocar, and two 5-mm subcostal trocars. The gallbladder was retrieved using a laparoscopic specimen bag through either.

Group U: gallbladder retrieved via the umbilical trocar, group E: gallbladder retrieved via the epigastric trocar.

After retrieval and hemostasis, the trocars were removed under direct laparoscopic vision. The umbilical fascia was closed using two interrupted polyglactin 910 sutures (Vicryl, Ethicon Inc., Edinburgh, Scotland); while the epigastric trocar fascia was left unsutured. Fascia closure practices were standardized and not related to group allocation. Total operation duration and gallbladder retrieval time were recorded.

All patients received paracetamol (Parol, Atabay İlaç, İstanbul, Türkiye) three times daily and tramadol (Contramal, Abdi İbrahim İlaç, İstanbul, Türkiye) twice daily for postoperative pain control. At 6 and 24 hours postoperatively, the Visual Analogue Scale (VAS) was used to assess pain in all patients with assistance from a ward nurse.

### Follow-up

Patients without complications were discharged on postoperative day 1. Those who developed complications were discharged upon resolution of their condition. Patients were followed for one year postoperatively. Patients presenting with hernia-related symptoms (e.g., bulge or pain) underwent ultrasonography (USG) at the time of symptom onset, while asymptomatic patients received routine USG at the six-month and one-year follow-ups. Radiologists performing USGs were not part of the study and their procedures were not standardized.

Incisional hernia was defined as a pathological fascial defect at a postoperative trocar site causing the protrusion of intraabdominal contents. Both clinically and radiologically diagnosed hernias were considered incisional hernias.

### Inclusion Criteria

- Age ≥18 years,
- Gallbladder stones,
- No known systemic comorbidities (e.g., cardiovascular, pulmonary, metabolic, or immunologic conditions).

### Exclusion Criteria

- Age <18 years,
- Open cholecystectomy or conversion from laparoscopy to open surgery,
- Acute cholecystitis,
- Prior intervention involving the common bile duct,
- Presence of clinical or radiologic diastasis recti,
- Presence of clinical or radiologic umbilical hernia.

### Primary and Secondary Outcomes

The primary outcome was an assessment of whether the site of gallbladder retrieval influenced the incidence of TSH following LC.

Secondary outcomes included assessing the relationship between retrieval site and postoperative pain (VAS scores) and identifying the risk factors associated with TSH.

### Statistical Analysis

Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY), and data visualizations were generated in RStudio version 4.2.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as mean ± standard deviation for normally distributed data or as median with min and maximum values for non-normally distributed data. Categorical data were analyzed using Fisher's exact or chi-square tests, and continuous variables were compared using Student's t-test or Mann-Whitney U test, depending on the distribution. Potential risk factors for incisional hernia were first evaluated using univariate logistic regression analyses. Variables with statistical significance ($p<0.05$) or clinical relevance were subsequently included in a multivariate logistic regression model to identify independent predictors of incisional hernia.

## Results

### Patient Characteristics

A total of 110 patients were enrolled, with 55 randomized to each group. Two patients in group U and one in group E required conversion to open surgery. Additionally, three patients in group U and four in group E were lost to follow-up. These 10 patients were excluded from the final analysis. The study flowchart summarizing patient enrollment, randomization, and outcomes is presented in Figure 1.

Baseline characteristics including age, gender distribution, previous abdominal surgery, chronic cough, and urgency of surgery were comparable between groups. The mean age was slightly higher in the umbilical group (51.68±15.66 years), compared to the epigastric group (46.50±12.20 years), though this difference did not reach statistical significance (p=0.068). Body mass index (BMI) and abdominal circumference were similar between groups (p=0.381 and p=0.475, respectively) (Table 1).

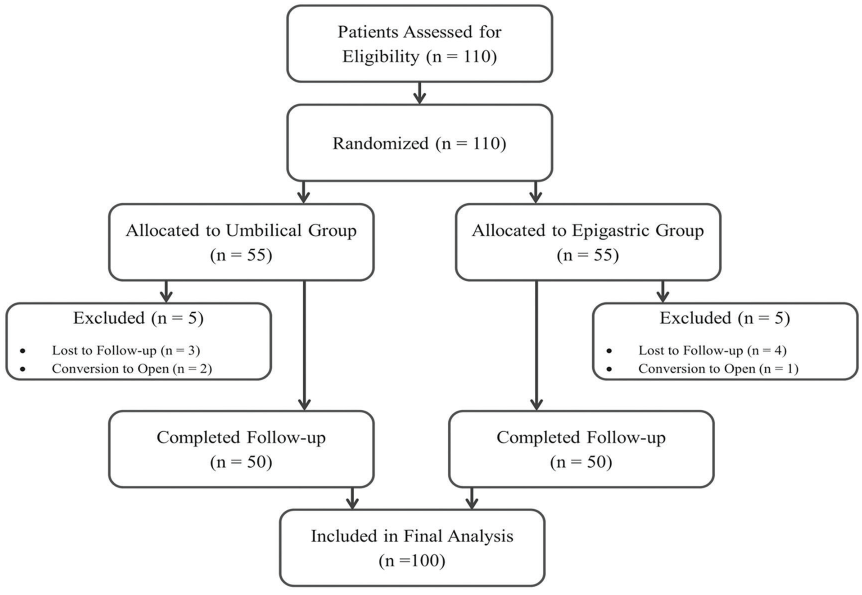



**Figure 1.** Flowchart of the study

**Table 1. Patient demographics**

| Variable | Category | Umbilical (n=50) | Epigastric (n=50) | p-value |
|---|---|---|---|---|
| Gender | Male | 15 | 9 | 0.241[α] |
| | Female | 35 | 41 | |
| Previous surgery | None | 32 | 29 | 0.682[α] |
| | Lower abdomen | 18 | 20 | |
| | Upper abdomen | 0 | 1 | |
| Chronic cough | No (0) | 46 | 49 | 0.362[α] |
| | Yes (1) | 4 | 1 | |
| | | **Mean ± SD** | **Mean ± SD** | |
| Age (years) | | 51.68±15.66 | 46.50±12.20 | 0.068[β] |
| Body mass index (kg/m$^2$) | | 28.50±4.73 | 29.36±5.01 | 0.381[β] |
| Abdomen circumference (cm) | | 98.70±14.60 | 96.44±16.85 | 0.475[β] |

Statistical significance at $p<0.05$. SD: Standard deviation, [α]: Fischer's exact chi-square test, [β]: Student's t-test

### Perioperative Outcomes

Median calculus diameter, operative duration, and extubation time did not differ significantly between the two groups. However, gallbladder retrieval time was significantly longer in the umbilical group compared to the epigastric group (p=0.013). Postoperative pain, assessed using VAS, was significantly lower at 6 hours in the umbilical group (p=0.027), while 24-hour scores were similar (p=0.285) (Table 2). Figure 2 presents raincloud plots illustrating the distribution of perioperative outcomes across the study groups.

### Incisional Hernia Rates

TSH occurred in 6 patients (12%) in the umbilical group and 5 patients (10%) in the epigastric group, with no statistically significant difference between groups (p=0.749; p=1.00 with Yates' correction). All hernias

**Table 2. Perioperative comparisons**

| | Median (min.-max.) | Median (min.-max.) | Rank (umbilical vs. epigastric) | p-value |
|---|---|---|---|---|
| Calculus diameter (mm) | 11 (1-30) | 13 (1-35) | 47.04 vs. 53.96 | 0.231 |
| Operation time (minutes) | 60 (19-110) | 55 (25-120) | 54.87 vs. 46.13 | 0.131 |
| Gallbladder retrieval time (minutes) | 3 (1-6) | 3 (1-5) | 57.41 vs. 43.59 | **0.013** |
| 6-hour VAS | 4 (2-7) | 4 (2-7) | 44.45 vs. 56.55 | **0.027** |
| 24-hour VAS | 3 (1-6) | 3 (1-6) | 47.51 vs. 53.49 | 0.285 |
| Externation time (hour) | 23 (14-96) | 23 (16-47) | 49.32 vs. 51.62 | 0.635 |

Mann-Whitney U test. Statistical significance at p<0.05. Min.: Minimum, Max.: Maximum, VAS: Visual Analogue Scale

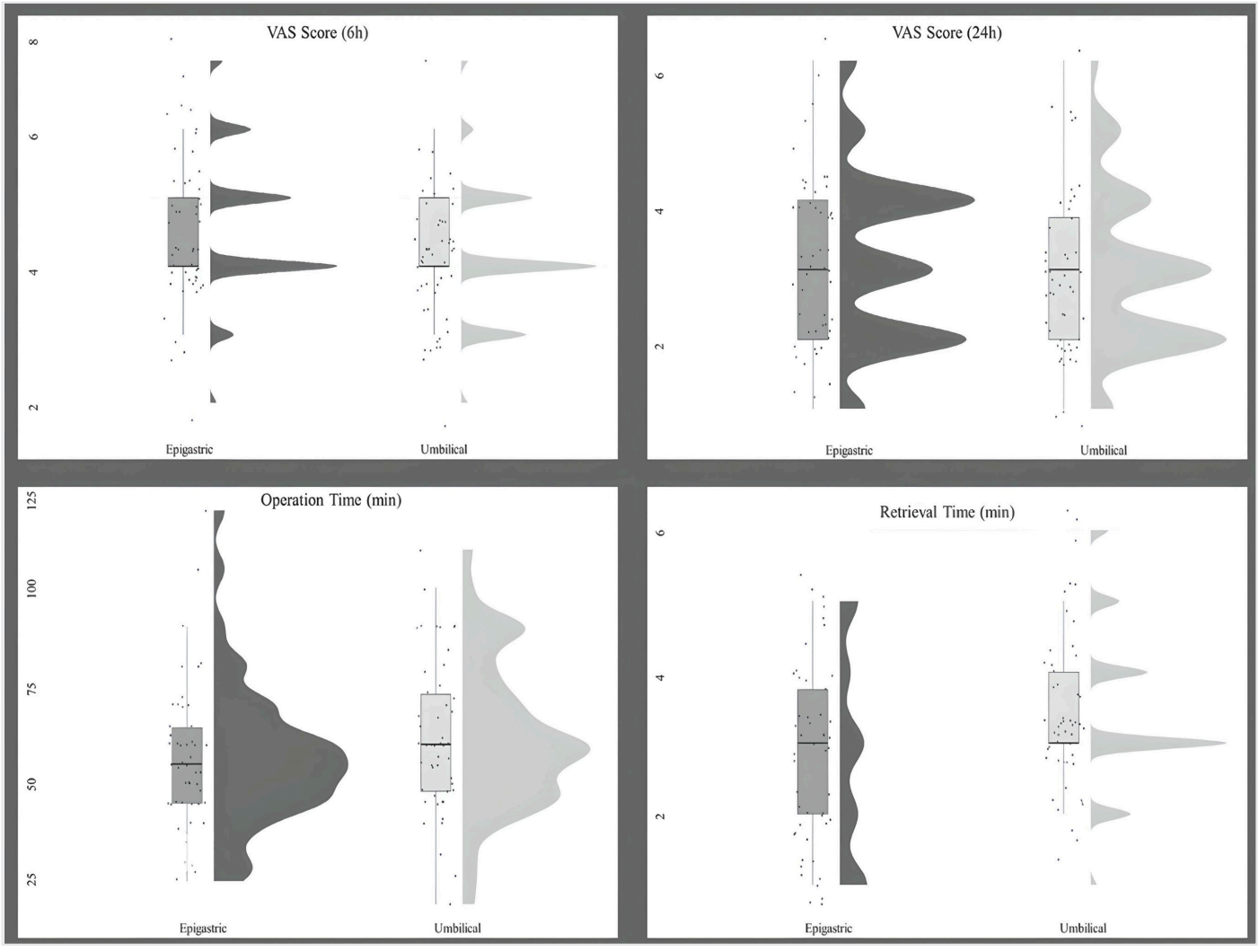



**Figure 2.** Top row: Visual Analogue Scale (VAS) scores at 6 hours and 24 hours postoperatively. Bottom row: total operation time and gallbladder retrieval time. Each plot displays individual data points, boxplots, and density distributions
Min: Minutes

were located at the umbilical trocar site, irrespective of the retrieval route (Table 3).

### Risk Factor Analysis

Univariate logistic regression identified two significant predictors of incisional hernia. Longer gallbladder retrieval time was associated with a lower risk of hernia [odds ratio (OR) =0.636, 95% confidence interval (CI): 0.445-0.909, p=0.013], while extraction site widening showed a trend toward increased hernia risk (OR =2.698, p=0.130), though this did not reach statistical significance. Age demonstrated a borderline association with decreased hernia risk (p=0.071). Other factors such as BMI, abdominal circumference, previous surgery, chronic cough, and operation duration were not significantly associated with hernia development.

In the multivariate model, which included variables with clinical relevance or statistical significance, extraction site widening was identified as an independent risk factor for incisional hernia (OR=4.080, 95% CI: 1.001-16.640, p=0.050). Gallbladder retrieval time was no longer statistically significant (p=0.069), and neither age nor operation time showed any meaningful association. Figure 3 displays a dot and whisker plot representing the univariate analysis of all evaluated risk factors for incisional hernia. Univariate and multivariate analysis results are summarized in Table 4.

Given that all incisional hernias in our cohort occurred at the umbilical trocar site, a subgroup analysis was performed to evaluate the effect of extraction site widening specifically in patients who underwent umbilical gallbladder retrieval. Logistic regression analysis demonstrated that extraction site widening was significantly associated with an increased risk of TSH in this group (p=0.014). The odds of developing a hernia were approximately 10.6 times higher (OR=10.571, 95% CI: 1.613-69.267) in patients with widened extraction sites compared to those without.

**Table 3. Incisional hernias**

| | | Incisional hernia | | Incisional hernia location | | p-value |
|---|---|---|---|---|---|---|
| | | No | Yes | Umbilical | Epigastric | |
| Extraction site | Umblical | 44 | 6 | 6 | 0 | p=1.00 |
| | Epigastric | 45 | 5 | 5 | 0 | |

Fishers Exact test. Statistical significance at p<0.05

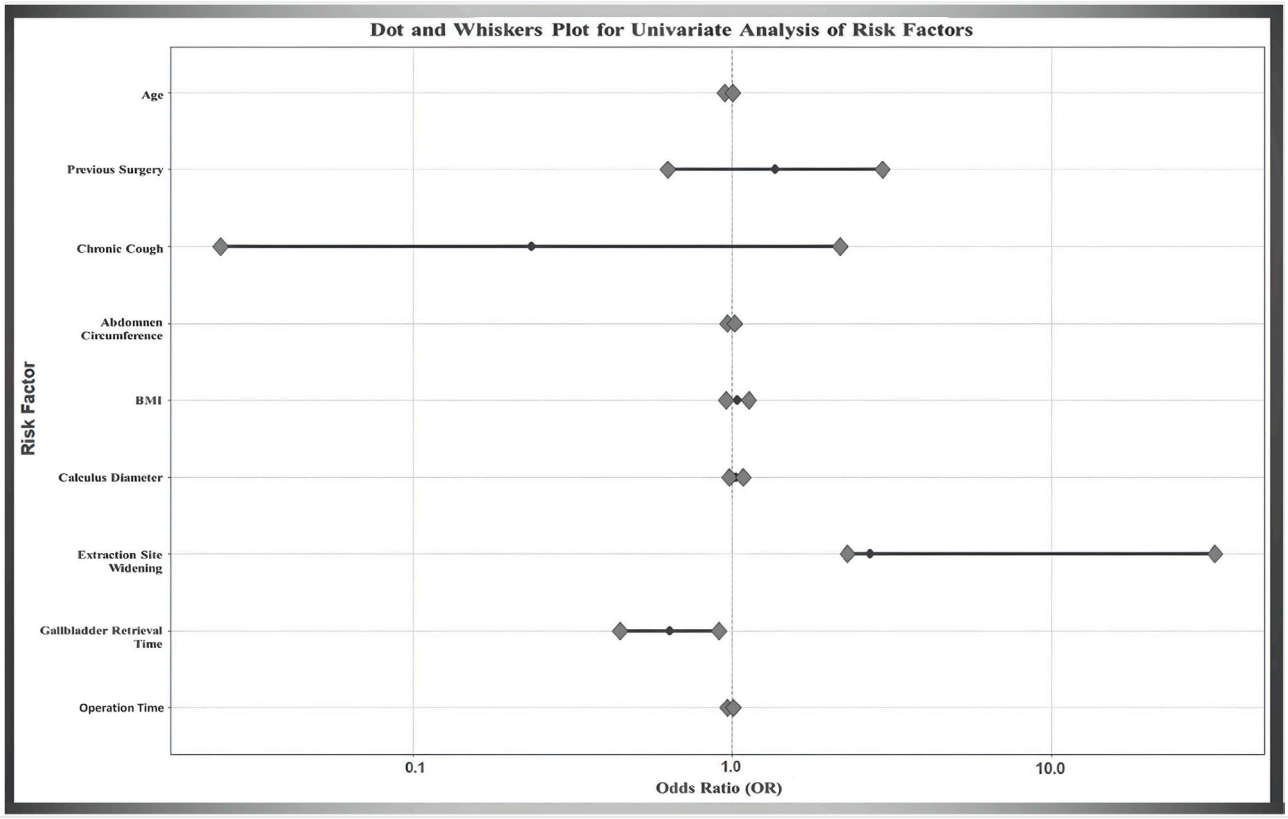



**Figure 3.** Each point represents the OR for a given variable, with horizontal lines indicating the 95% confidence intervals. Diamond markers highlight the confidence interval boundaries. Variables assessed include patient demographics, clinical characteristics, and intraoperative factors. Extraction site widening showed a strong association with TSH risk, while longer gallbladder retrieval time appeared protective
BMI: Body mass index, OR: Odds ratio, TSH: Trocar site hernias

**Table 4. Univariate analysis of risk factors associated with incisional hernia**

| | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | B | 95% CI | OR | p (Sig.) | B | 95% CI | OR | p (Sig.) |
| Age (years) | -0.027 | 0.946-1.002 | **0.974** | **0.071** | 0.002 | 0.952-1.055 | 1.002 | 0.935 |
| Previous surgery | 0.309 | 0.629-2.951 | 1.362 | 0.434 | | | | |
| Chronic cough | -1.449 | 0.025-2.178 | 0.235 | 0.202 | | | | |
| Abdomen circumference | -0.009 | 0.966-1.016 | 0.991 | 0.471 | | | | |
| BMI (kg/m$^2$) | 0.037 | 0.956-1.126 | 1.038 | 0.377 | | | | |
| Calculus diameter | 0.029 | 0.981-1.080 | 1.029 | 0.241 | | | | |
| Extract site widening | 0.993 | 2.29732.496 | **2.698** | **0.130** | 1.406 | 1.001-16.640 | **4.080** | **0.050** |
| Gallbladder retrieval time | -0.452 | 0.445-0.909 | **0.636** | **0.013** | -0.690 | 0.273-1.050 | 0.535 | 0.069 |
| Operation minutes | -0.015 | 0.964-1.007 | **0.985** | **0.177** | 0.005 | 0.971-1.040 | 1.005 | 0.772 |

Univariate analysis. Statistical significance at $p<0.005$
CI: Confidence interval, OR: Odds ratio, BMI: Body mass index

## Discussion

TSHs are recognized complications of laparoscopic procedures, with incidence rates reported to range from 0.2% to 25%, depending on factors such as trocar size, site, patient comorbidities, and follow-up duration (4,11). One of the largest cohorts reported a 2% TSH rate within 5 years after LC (12).

The umbilical site, particularly when a 10-mm trocar is used, is the most common location for TSH development (13). Anatomically, the umbilicus represents a naturally weakened area of the linea alba, with a congenital fascial defect that originally allowed the passage of the umbilical cord. The periumbilical arteries, which traverse the single-layer fascia, further compromise its structural integrity (14). Furthermore, the presence of diastasis recti may contribute to weaken the layers and has been reported as a strong risk factor for TSH (15). Consequently, creating an artificial fascial defect at this already vulnerable site predisposes patients to TSH formation. Intraoperative maneuvers, particularly those involving increased force or fascial enlargement during organ extraction, may further stress the umbilical fascia. Several studies have shown that using the umbilical trocar for specimen retrieval is associated with an increased risk of TSH (16-18). A recent retrospective study of more than 2,300 patients reported similar results, with umbilical specimen retrieval being associated with more TSH (3.2%) compared to epigastric retrieval (0.7%) (19). In our study, all observed TSHs occurred at the umbilical trocar site, in line with existing literature.

Another concern with using the umbilical site for extraction is potential operative delay. Switching camera positions, reorienting the visual field, and adapting to an altered surgical axis may contribute to increased operative time. The literature on this topic is mixed, with some studies reporting no difference in retrieval time (17,18,20,21), others favoring epigastric extraction (22), and some still supporting umbilical use (16). Our findings are consistent with those demonstrating shorter retrieval times associated with the epigastric approach.

Postoperative pain is a major determinant of patient satisfaction and is one of the leading causes of readmission following LC (23). While some studies suggest that umbilical extraction results in less postoperative pain (18,20,22), others, including a recent meta-analysis, find no significant difference between extraction routes (17). Anand et al. (20) demonstrated higher VAS scores at all postoperative time points in patients undergoing epigastric extraction. In our cohort, umbilical extraction was associated with significantly lower VAS scores at 6 hours postoperatively, and non-significantly lower scores at 24 hours. This is consistent with most previous reports. Higher pain scores associated with epigastric extraction may be attributed to greater muscle disruption or tension in the upper abdominal wall.

However, postoperative pain is multifactorial and influenced by various elements such as patient pain threshold, anxiety levels, intraoperative medication use, and surgical manipulation technique (24). As this study did not account for all potential contributors to postoperative pain, our findings should be interpreted with caution. A definitive conclusion regarding the impact of retrieval site on postoperative pain would require a randomized controlled trial designed to control for these confounding variables.

Risk factors for TSH include older age, obesity, diabetes, and chronic pulmonary disease (25-27). Regardless of patient-related risks, current surgical guidelines recommend fascial closure for all trocar sites ≥10 mm to reduce TSH incidence (28,29). In our study, the only variable significantly associated with TSH formation was fascial widening during extraction. This observation is consistent with previous findings that larger trocars are linked to increased hernia rates (7,30). In contrast, a recent meta-analysis comprising more than 7,000 patients reports that there was no association between incision enlargement and TSH risk. However, there is a paucity of randomized controlled trials evaluating the isolated effect of fascial dilation on hernia formation. Notably, TSH rates as low as 0.08% have been reported with the use of 5-mm trocars, suggesting that when feasible, use of a 5-mm umbilical port with a 5-mm laparoscope may reduce TSH risk.

Given that all incisional hernias in this study occurred at the umbilical trocar site, a subgroup analysis was conducted to specifically assess the impact of extraction site widening among patients who underwent umbilical gallbladder retrieval. In this subgroup, extraction site widening was significantly associated with an increased risk of incisional hernia.

This finding strengthens the hypothesis that even in the absence of large trocar sizes or other systemic risk factors, mechanical disruption of the umbilical fascia substantially increases hernia risk. While the umbilicus is already anatomically predisposed to weakness, our results suggest that technical factors-specifically fascial handling-play a decisive role in postoperative hernia formation. Given that all hernias in our study occurred at the umbilical site, minimizing fascial manipulation during retrieval should be a priority. This may include avoiding unnecessary enlargement of the port and considering alternative extraction routes in appropriate patients.

### Study Limitations

While larger series and meta-analyses on TSH exist, our study adds value through strict standardization of surgical technique and routine USG screening, which minimized diagnostic bias. Although an a priori power analysis was conducted, the relatively small sample size limits statistical power. Larger, multicenter studies are needed to confirm our findings and support broader clinical application.

## Conclusion

Epigastric extraction was not associated with an increased risk of TSH in our study. Additionally, it was linked to shorter operative times compared to umbilical extraction. However, this benefit comes at the cost of slightly higher postoperative pain. Given this trade-off, epigastric extraction may be preferred in cases where reduced operative time is a priority, and effective pain management strategies are readily available. Future studies should investigate the impact of using a 5-mm camera and trocar at the umbilical site on TSH formation, as this approach may offer a balance between safety and patient comfort.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, Clinical Research Ethics Committee (approval number: 106, date: 31.03.2022).

**Informed Consent:** Written informed consent was obtained from all patients for participation in and publication of the study.

### Footnotes

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

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

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# Medial Meniscus Extrusion is Correlated with Varus Alignment in Patients Without Meniscus Tear

Fatih Barça[1], Albert Çakar[2], Ekin Barış Demir[1], Coşkun Genç[1], Mutlu Akdoğan[1], Yalım Ateş[1], Halis Atıl Atilla[1]

[1]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Orthopedics and Traumatology, Ankara, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye

## ABSTRACT

**Introduction:** There is a well-established connection between medial meniscus lesions and varus leg alignment, and medial meniscus lesions like posterior root tears are known to cause meniscus extrusion. However, the evidence regarding the relation between varus alignment and meniscus extrusion in knees without meniscus lesions is controversial. Our study aimed to evaluate the correlation between varus alignment and meniscus extrusion in knees without meniscus lesions.

**Methods:** One hundred thirty knees of 113 patients, with a mean age of 48.8±11.3 years, 33.8% male, without meniscus lesions and with long leg radiographs and knee magnetic resonance imaging, were retrospectively analyzed. Extrusion was considered positive if it exceeded 3 mm. Varus malalignment of legs was grouped as mild (0°-4.9°), moderate (5°-9.9°), and severe (≥10°) according to hip-knee-ankle (HKA) angle measurement, and it was also noted that bone edema in the medial compartment was present. The correlation among extrusion measurement, varus malalignment HKA, and bone marrow edema was analyzed.

**Results:** Fifty-seven knees (43.8%) had extruded menisci. The mean HKA angle was 4.6±3.6. 82 legs (63.1%) had mild, 37 legs (28.5%) had moderate, and 11 legs (8.5%) had severe varus. Bone marrow edema was noted in 88 knees (66.7%). Relationship between extrusion and severity of varus ($p<0.001$) and bone marrow edema ($p<0.001$) was significant. The extent of meniscal extrusion showed significant correlation with HKA angles (coefficient =0.481, $p<0.001$).

**Conclusion:** Varus malalignment was revealed to correlate with medial meniscus extrusion in knees without meniscal damage.

**Keywords:** Meniscus, varus, extrusion, knee, alignment

## Introduction

Menisci are fibrocartilaginous, wedge-shaped, and load-absorbing structures composed of type I collagen, elastin, proteoglycans, glycoproteins, and water. In addition to the balanced transmission of the load in the knee, it has functions such as stability, proprioception, and smoothness of motion (1).

The arrangement of the fibres in the normal meniscus structure enables the conversion of compressive loads into circular loads (i.e. hoop stress). It also eliminates the mismatch between the proximal tibia and the distal femur. This prevents degeneration of the articular cartilage. The relationship between disruption of normal meniscal structure and degenerative changes in articular cartilage (2), subchondral lesions, bone marrow edema (3), and alignment changes such as narrowing of the joint space (4) has been demonstrated.

Menisci can extrude from the tibial plateau within physiologic limits in the absence of degeneration, joint pathologies, and malalignment (5). Other than this, extrusion can be present in conditions that disrupt the meniscal structure, such as meniscal tears or degeneration (6). More than a 3 mm extension (1,7) is considered an extruded meniscus. Extruded meniscus is an independent risk factor for articular cartilage degeneration (8).

Varus deformity is a predisposing factor for articular cartilage degeneration, meniscal damage and osteoarthritis (9). The pathogenesis of this condition is due to the mechanical axis of the leg lying more medially and the load on the medial aspect of the knee increasing beyond physiologic limits (10). Meniscal extrusion may be expected in varus deformity due to disruption of the joint load distribution. However, there is no consensus on the relation between extrusion and varus alignment, besides meniscal lesions such as meniscal root tears or degeneration (11-13).

**Address for Correspondence:** Fatih Barça MD, University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Orthopedics and Traumatology, Ankara, Türkiye
**E-mail:** fatihbarca@hotmail.com **ORCID ID:** orcid.org/0000-0002-8167-6146

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The aim of this study was to assess the relationship between meniscal extrusion and varus alignment in patients with varus deformity without medial meniscal tear or degeneration. We hypothesised that varus malalignment would lead to meniscal extrusion.

## Methods

In this study, 459 adult patients (ages 18-65) with knee magnetic resonance (MR) imaging and long leg radiographs (LLR) who applied to the orthopaedics and traumatology outpatient clinics of our hospital between March and June 2023 were retrospectively analyzed. Exclusion criteria were as follows: patients with meniscal tear on MR imaging, patients with symptoms and/or examination findings that may be related to meniscus in clinical examinations (snapping sensation in the knee joint, positive McMurray sign, pain with deep pressure to medial joint space), patients with valgus alignment on LLR, patients with a history of ipsilateral surgery, and patients without optimal imaging. Finally, 130 knees (67 right, 63 left) of 113 patients (44 males, 69 females, mean age 48.8±11.3) were enrolled (Table 1). The study flowchart is shown in Figure 1.

The LLR were taken with the patient standing, knees in full extension, 100 cm from the beam source, the detector parallel to the ground, and the centre of the radiograph directed at the patellofemoral joint (14). We determined the optimal radiographs as those where the patella was facing forward and both hip and ankle joints were seen. Measurements were performed using the hospital picture archiving and communication system [Innbiotec (DICOM) Viewer, Innbiotec Software, Dubai, UAE]. Hip-knee-ankle (HKA) angle measurement (Figure 2) was used to evaluate leg alignment. According to the HKA angle, patients were divided into three groups: mild (0°-4.9°), moderate (5°-9.9°), and severe (≥10°) varus (15).

MR imaging of the knee was obtained in knee extension as a standard procedure. The distance from the end of the medial tibial plateau to the border of the medial meniscus was measured in the midcoronal plane on coronal T2 MR slices (Figure 3). A distance of more than 3 mm was classified as extruded meniscus (7). The presence of bone marrow oedema in the medial compartment was also noted. All radiographic measurements were performed twice at three-week intervals by two observers blinded to the diagnosis.

### Ethical Approval

This study was performed in accordance with the Helsinki Declaration. Consent was gathered from each of the participants enrolled in our study. The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval number: AEŞH-EK1-2023-531, date: 22.11.2023).

### Statistical Analysis

Statistical evaluation of the data was performed using statistical package for the social sciences (Windows) 20.0. Conformity to the normal distribution was examined by the Kolmogorov-Smirnov test. The chi-square test was used to analyze categorical data. Correlation analyses were performed using the Pearson correlation test. Inter- and intra-observer reliability of measurements was evaluated using intraclass correlation coefficient (ICC) and the results of reliability analyses were presented as mean ICC. Post-hoc power analysis was performed using G*power version 3.1.9.6 (Franz Paul, Kiel, Germany). Data were analyzed at a 95% confidence level and tests were considered significant if the p-value was less than 0.05.

## Results

The mean ICC of the observations was 0.92 for HKA angles and 0.93 for meniscus extrusion measurements, and the mean Cohen's kappa coefficient was 0.95 for bone bruise. The mean HKA angle of 130 legs was 4.6±3.6. Eighty-two legs (63.1%) had mild, 37 legs (28.5%) had moderate, and 11 legs (8.5%) had severe varus. The mean meniscus extrusion measure in knee MR imaging was 2.9±1.9 mm. With the predefined cut-off of 3 mm, 57 knees (43.8%) did and 73 knees (56.2%) did not have extruded menisci.

Correlation analysis revealed a significant positive relationship between HKA angles and meniscus extrusion (coefficient =0.481, $p<0.001$). Also, when categorical data were analyzed, a significant difference was observed between varus severity groups in terms of the presence of meniscus extrusion ($p<0.001$).

Bone marrow oedema in the medial compartment was present in 88 knees (66.7%). There was a significant relationship between the presence of meniscus extrusion and bone marrow oedema ($p<0.001$). Data and results of statistical analyses are presented in Table 2. Post-hoc power analysis was performed with a significance level (alpha) set to 0.05 and revealed a power of 99.97% for the study.

## Discussion

Although it has been previously shown in the literature that varus deformity is a risk factor for meniscal lesions (16) and meniscal lesions cause meniscal extrusion (6), our study revealed that varus deformity has a direct and significant relationship with meniscal extrusion without meniscal tear.

The meniscus bears 40-70% of the load on the knee and is responsible for the balanced distribution of "hoop stress" through the placement of collagen fibres in the meniscal structure (7). Disruption in this collagen

**Table 1. Symptoms of patients**

| Symptoms of patients | n (%) |
|---|---|
| Anterior knee pain | 67 (51.6%) |
| Swelling/effusion | 30 (23.1%) |
| Lateral knee pain | 25 (19.2%) |
| Palplable mass | 3 (2.3%) |
| No active symptoms (i.e. follow-up of a soft tissue lesion) | 3 (2.3%) |
| Patellar instability | 2 (1.5%) |

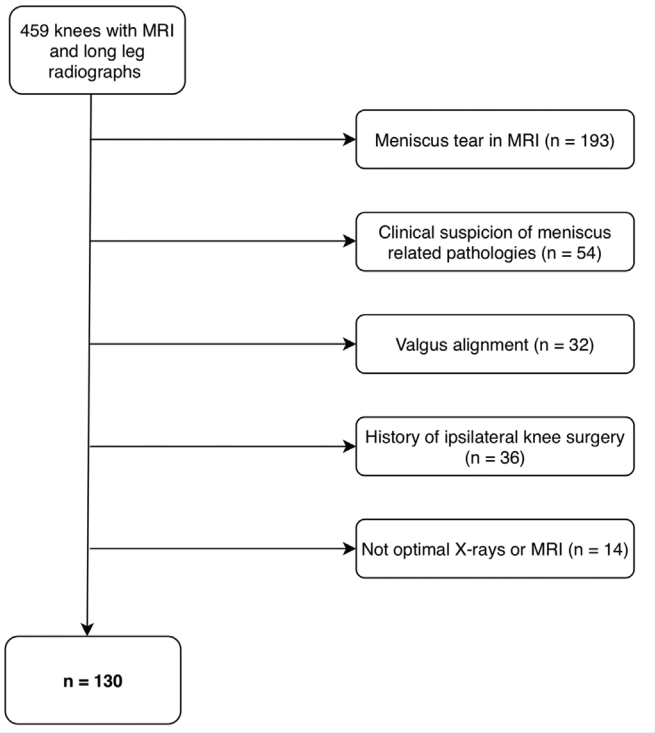



**Figure 1.** Study flowchart
MRI: Magnetic resonance imaging

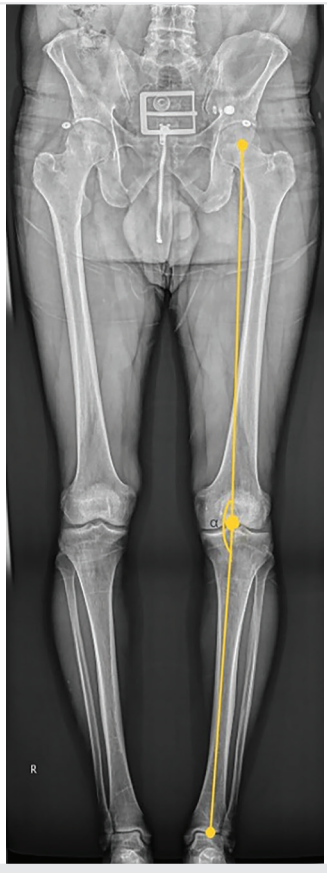



**Figure 2.** Hip-knee-ankle angle was measured in long leg radiographs as the angle between mechanical axes of femur and tibia (180-alpha)
R: Right

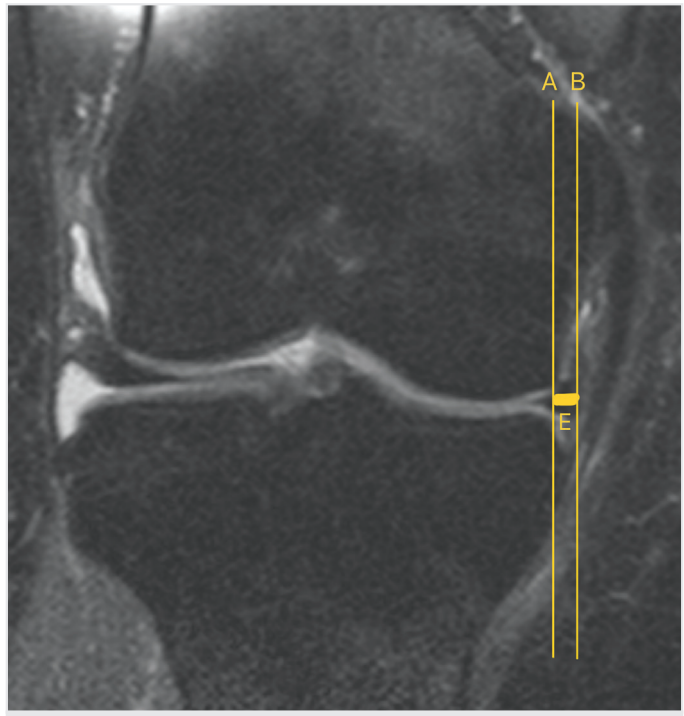



**Figure 3.** Meniscal extrusion (E) was measured in midcoronal MRI slice as the distance between the most medial points of medial plateu (A) and medial meniscus (B)
MRI: Magnetic resonance imaging

structure impairs the load balance and may lead to joint degeneration. The relationship between meniscal lesions and joint degeneration has been previously reported in the existing literature (2,17). The medial meniscus is more frequently affected due to its location, the amount of load it carries, and the fact that it has a tighter connection with the structures in the medial part of the joint than the lateral part (18) through structures such as the meniscotibial and meniscofemoral ligaments. It plays a greater role in joint degeneration when damaged (7).

Meniscal extrusion can be defined as the displacement of the circumferential fibres from the meniscotibial compartment, as a result of their inability to bear the load (18). When meniscal extrusion was first described, it was suggested that it did not cause a pathology on its own, and was a consequence of other pathologies (19). Recent studies have demonstrated a positive relationship between meniscal extrusion and cartilage loss (20), osteophytes (8), subchondral cysts, and bone marrow oedema (21). Biomechanically, meniscal extrusion and load on the medial compartment are correlated (22).

Nevertheless, it has been reported (1,5) that some amount of meniscal extrusion, not exceeding the threshold value, may occur in knees without signs of degeneration and may not always be associated with osteoarthritis (1,5), although the cause has not been fully elucidated. Meniscotibial and meniscofemoral ligament lesions may lead to meniscal extrusion in the absence of tears (1). It has also been suggested that lesions of these ligaments are a predisposing factor for root tears (23). Current literature suggests that severe meniscal extrusion is a pathologic condition by itself and proposes various treatment options (24,25). Furthermore, as it has been shown that meniscal extrusion can progress even after the repair of a meniscal root tear (26), it remains uncertain

**Table 2. Demographic data and results of analyses**

| | Extrusion <3 mm (n=73) | Extrusion ≥3 mm (n=57) | p value |
|---|---|---|---|
| Age (years) | 44.2±11.1 | 54.6±8.6 | <0.001 (1) |
| Sex | | | 0.554 (2) |
| Male | 28 (38.4%) | 19 (33.3%) | |
| Female | 45 (61.6%) | 38 (66.7%) | |
| HKA angle | 3.15±2.4° | 6.64±3.97° | <0.001 (1) |
| Severity of varus | | | <0.001 (2) |
| Mild | 59 (80.8%) | 23 (40.4%) | |
| Moderate | 14 (19.2%) | 23 (40.4%) | |
| Severe | 0 (0%) | 11 (19.2%) | |
| Bone marrow edema present | 9 (12.3%) | 33 (57.9%) | <0.001 (2) |

HKA: Hip-knee-ankle angle

whether additional predisposing factors such as malalignment may play a role in this condition.

It has been shown that medial meniscal extrusion can cause medial osteoarthritis accompanied by varus deformity (18). In addition, Crema et al (11). examined cases with and without osteoarthritis and concluded that varus alignment had an independent association with meniscal extrusion, but it was not clear which meniscal lesion was associated with the development of osteoarthritis. However, it should be added that in this study, patients with meniscal tears, including meniscal root tears, were also included in the varus deformity group. In addition, Erquicia et al (13). found no relationship between meniscal extrusion and limb alignment. In our study, unlike a previous study, we found a direct correlation between varus deformity and meniscal extrusion ($p<0.001$).

Problems affecting the medial compartment of the knee joint cause bone marrow oedema, especially in the medial condyle (3,27). The relationship between bone marrow oedema, which can be spontaneous, mechanical, or reactive (27), and meniscal extrusion has been previously demonstrated (3). In our study, we found that meniscal extrusion and bone marrow oedema were more frequently observed together in patients without meniscal tears or degeneration ($p<0.001$). This may be interpreted as an indication, that the mechanical load on the medial compartment of the knee joint increases due to extrusion. While this relationship has been demonstrated by biomechanical studies for varus malalignment (16), biomechanical studies on the increased mechanical load as a direct result of meniscal extrusion are insufficient.

### Study Limitations

Other than its retrospective design, the limitations of our study include that the symptoms and/or clinical findings of the patients were not correlated with radiographic findings. However, if this examination had been performed, it could have led us to obtain data unrelated to the purpose of the study. In addition, the use of data from a variety of MR imaging devices in the measurements can be considered another limitation. The large number of observations and high interobserver agreement may partially overcome the possible effects of this disadvantage. Evaluating meniscal extrusion with MR images taken without axial loading may affect the results. However, it is currently believed that the gold standard evaluation method for meniscal extrusion is MR imaging, and weight-bearing imaging such as ultrasonography may not provide adequate quality and quantitative measurements (28).

## Conclusion

Our study found that varus alignment, which is one of the controversial risk factors for meniscal extrusion, may be directly associated with meniscal extrusion in patients without meniscal tears. There is also a positive correlation between extrusion of medial meniscus and bone oedema in the medial compartment of the knee joint.

### Ethics

**Ethical Approval:** The study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval number: AEŞH-EK1-2023-531, date: 22.11.2023).

**Informed Consent:** Retrospective study.

### Footnotes

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

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

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# University Students Approach to Human Papilloma Virus and Vaccine, Knowledge Level Analysis

Elif Uçar[1], Melih Bestel[1], Seda Aşcı[2]

[1]İstanbul Esenyurt University Faculty of Health Sciences, Private Esencan Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye
[2]İstanbul Esenyurt University Vocational School of Health Services, İstanbul, Türkiye

## ABSTRACT

**Introduction:** In this study, the aim was to evaluate the level of knowledge of university students about human papilloma virus (HPV) and HPV vaccine, to determine their attitudes towards HPV vaccination and the obstacles they face, and to emphasise what needs to be done to increase awareness.

**Methods:** In this descriptive study, participants were administered a structured questionnaire containing questions on HPV infection, types of vaccines, age ranges for vaccination and vaccine efficacy. In addition, the effect of factors such as attitudes towards vaccination, sources of information and the cost of vaccination was also evaluated.

**Results:** The results showed a lack of knowledge about HPV and HPV vaccines among university students. Most of the participants were not sufficiently familiar with the vaccine, and although they had information about HPV infection, they were hesitant about the vaccine's protective benefits. Cost, lack of information, and confidence in the vaccine were the main reasons for not getting vaccinated.

**Conclusion:** Our study revealed that awareness of HPV vaccination among university students is low and the cost of the vaccine is an important barrier. To implement an effective HPV vaccination programme, awareness-raising activities should be carried out, especially using peer networks and social media. In addition, awareness can be raised through educational programmes and curriculum arrangements.

**Keywords:** Human papilloma virus, vaccine, university student, social awareness, cost

## Introduction

Human papilloma virus (HPV) and its vaccine, which is closely related to public health, are of critical importance, especially for the young population. HPV is a public health problem that is particularly prevalent in young people aged 15 to 24 years in the United States, with an estimated 4.5 million new cases reported each year. This constitutes almost half of the new infections reported in this age group (1). In addition to the high infection rates of HPV, the asymptomatic course of many strains may also cause this situation (2). In addition, it has been demonstrated in studies that those who have been infected may not disclose this situation because they are afraid of the social stigma, and therefore the prevalence of the disease may be higher than detected (3,4).

According to studies conducted to examine HPV and the effects of this virus on health, a lack of knowledge about this virus and its impact was found among university students and young adults (5). In a study, it was shown that male university students, who were found to lack information, could benefit greatly from health education (6). In addition, a study revealed that 80% of university students who were hesitant about vaccination were concerned about vaccine safety and therefore avoided it (7).

Studies have shown that educational planning will increase awareness, and acceptance of HPV and HPV vaccine among young people and the rest of society. This planning is expected to be an incentive for HPV vaccination (8,9).

Issues such as the approach of parents, hesitations about vaccine safety, and the effects of the disease on sexuality and health are factors that determine the approach to HPV vaccination. Studies have shown that parents' approach to vaccination affects young people's confidence in vaccination, and there is a positive correlation between the two approaches. Children of parents with a positive approach to vaccination were more willing to be vaccinated (10,11). Studies have shown that visits to regular healthcare services, friends, and communication through social media channels, and the use of reminder features of mobile applications increase awareness of infection and encourage vaccination (11-13).

**Address for Correspondence:** Elif Uçar MD, İstanbul Esenyurt University Faculty of Health Sciences, Private Esencan Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye
**E-mail:** eliflyy@hotmail.com **ORCID ID:** orcid.org/0000-0001-5302-4688

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This study aimed to investigate the awareness of university students about HPV and the HPV vaccine, as well as to determine the level of knowledge.

## Methods

Three hundred eighty-seven students studying at a private university in 2024 were included in the study. The study was prospectively designed, and the participants were randomly and voluntarily selected. The students were first informed about the study, their consent for participation was obtained, and then the questionnaire was applied. The results were recorded. There were no exclusion criteria in the study. The study was approved by the İstanbul Esenyurt University Ethics Committee (approval number: 03, date: 05.12.2023).

### Statistical Analysis

In the study, descriptive statistics are at the forefront. Statistical analyses were performed using SPSS (IBM SPSS Statistics 27) package program. Frequency tables and descriptive statistics were used to interpret the findings.

## Results

Three hundred fifty-five (91.7%) were in the 18-30 age group, 307 (79.3%) were female, and 382 (98.7%) lived in the city. Two hundred seven (53.5%) had a monthly income of <10,000 TL, 211 (54.5%) had health insurance, and 331 (85.5%) had not received the HPV vaccine (Table 1).

### Level of Knowledge

58.7% of the students knew that cervical cancer was the most common gynaecological cancer. Additionally, 45.5% knew that smoking was a risk factor for this type of cancer. 51.4% of the students knew that HPV transmission could be prevented by barrier methods such as condoms. 67.2% did not know that oral contraceptives and monthly injections were not protective. 35.4% of the students knew that HPV was responsible for most of the cervical cancer cases in our country. Only 27% of the students knew that there is a screening programme for cervical cancer in our country. 26.6% of the students knew that the HPV vaccine provides close to 100% virus type-specific protection from HPV infection. 51.4% of the students knew that vaccination protects both men and women. 63% of the students did not know that there were three types of vaccines in our country (Table 2).

### Willingness

In addition, the students' perspective on vaccination was evaluated. Only 14.5% of the students were vaccinated (Table 1). 52.5% of the students said that they would have the vaccine, 55.8% said that they would have it for their daughters, and 53.2% said that they would have it for their sons. While 30.5% of the students stated that they would have the vaccine even if they had to pay for it, this rate increased to 58.1% if the vaccine was covered by insurance reimbursement (Table 3).

### Motivators

52.2% of the patients stated that they learnt about the vaccine from social media, 6.5% from doctors or health workers. Among the students, 7.2% stated that the vaccine was protective against condyloma, 18.6% against cancer, and 64.9% against both (Table 4).

## Discussion

In this study, the level of knowledge of university students about HPV and their attitudes towards vaccination was evaluated. In the results obtained, university students demonstrated a serious lack of information. In addition, it was observed that vaccination rates remained low due to the cost of the vaccine. Considering that infection in the young population can spread rapidly and become a public health problem, we think that vaccines should be included in the scope of social security, and that awareness should be raised through social media, friends, and planned health education.

HPV, which is of critical importance for the young population and adults in the reproductive period, is also a public health problem. The asymptomatic progression of HPV in many individuals makes this virus particularly concerning (2). The association of some types of the virus with cervical cancer is extremely important, especially. In a study conducted in the USA, the aim was to increase the level of knowledge of medical and dental students about HPV (14). In the same country, a survey conducted among women of reproductive age revealed that both the level of knowledge about HPV was low and that vaccination rates were inadequate (15). In a study conducted by Akçaoğlu et al. (16) in Türkiye, it was found that vaccination rates were quite low even in adults. Similarly, studies conducted in Algeria, Romania, and Morocco revealed that the level of knowledge of university students, high school students, parents, and healthcare professionals about HPV and the HPV vaccine was inadequate; it was emphasised that national vaccination programmes should target the young population and should be supported by educational policies (17-19). In our study, only 35.4% of university students were aware of the relationship between cervical

**Table 1. Demografic data**

| Variables (n=387) | n | % |
|---|---|---|
| **Age (years)** | | |
| Under 18 | 4 | 1.0 |
| 18-30 | 355 | 91.7 |
| 31-40 | 25 | 6.5 |
| 41-50 | 3 | 0.8 |
| **Gender** | | |
| Female | 307 | 79.3 |
| Male | 80 | 20.7 |
| **Region of residence** | | |
| City | 382 | 98.7 |
| Rural | 5 | 1.3 |
| **Monthly income level** | | |
| Less than 10,000 TL | 207 | 53.5 |
| 10,000-20,000 TL | 83 | 21.4 |
| More than 60,000 TL | 97 | 25.1 |
| **Health insurance** | | |
| Yes | 211 | 54.5 |
| No | 176 | 45.5 |
| **HPV vaccination** | | |
| Yes | 56 | 14.5 |
| No | 331 | 85.5 |

HPV: Human papilloma virus, TL: Turkish liras

**Table 2. HPV awareness levels**

| Variables | Yes | No | I don't know |
|---|---|---|---|
| Cervical cancer is the most common gynaecological cancer worldwide. | 227 (58.7%) | 48 (12.4%) | 112 (28.9%) |
| The prevalence of cervical cancer in Türkiye is lower than the world average. | 112 (28.9%) | 110 (28.4%) | 165 (42.7%) |
| The majority of cervical cancer cases are seen in developed regions. | 137 (35.4%) | 96 (24.8%) | 154 (39.8%) |
| A history of sexually transmitted diseases is a risk factor for cervical cancer. | 289 (74.7%) | 29 (7.5%) | 69 (17.8%) |
| Smoking is not a risk factor for cervical cancer. | 95 (24.5%) | 176 (45.5%) | 116 (30.0%) |
| Oral contraceptive use (birth control pill) is a risk factor for cervical cancer. | 135 (34.9%) | 90 (23.2%) | 162 (41.9%) |
| Having many births is protective against cervical cancer. | 102 (26.4%) | 136 (35.1%) | 149 (38.5%) |
| HPV transmission can be reduced by using barrier methods such as condoms. | 199 (51.4%) | 70 (18.1%) | 118 (30.5%) |
| HPV cannot be prevented by birth control methods such as birth control pills and monthly injections. | 127 (32.8%) | 111 (28.7%) | 149 (38.5%) |
| HPV has been detected in most of the cervical cancer cases. | 137 (35.4%) | 48 (12.4%) | 202 (52.2%) |
| HPV is a sexually transmitted infectious agent. | 237 (61.2%) | 73 (18.9%) | 77 (19.9%) |
| HPV can cause genital and extragenital (mouth. throat) warts. | 225 (58.1%) | 46 (11.9%) | 116 (30.0%) |
| There is no screening programme for cervical cancer in our country. | 99 (25.6%) | 105 (27.1%) | 183 (47.3%) |
| Pap-smear test and detection of high-risk HPV types are used in screening. | 148 (38.2%) | 69 (17.8%) | 170 (44.0%) |
| Screening reduces the incidence and mortality of cervical cancer. | 132 (34.1%) | 74 (19.1%) | 181 (46.8%) |
| HPV is not a serious enough infection to require vaccination. | 80 (20.7%) | 218 (56.3%) | 89 (23.0%) |
| The HPV vaccines are protective against some types of cancer in both men and women. | 199 (51.4%) | 65 (16.8%) | 123 (31.8%) |
| The virus type-specific protection of HPV vaccine in HPV infection is close to 100%. | 103 (26.6%) | 79 (20.4%) | 205 (53.0%) |
| The protection offered by the HPV vaccine against cervical cancer is around 70%. | 151 (39.0%) | 54 (14.0%) | 182 (47.0%) |
| The ideal age group recommended for HPV vaccination is 11-12 years. | 120 (31.0%) | 79 (20.4%) | 188 (48.6%) |
| HPV vaccine is included in the routine vaccination programme of the Ministry of Health. | 132 (34.1%) | 90 (23.3%) | 165 (42.6%) |
| HPV vaccines in Türkiye are of three types: 2, 4, 9-valent, and these vaccines are administered in 3 doses. | 143 (37.0%) | 26 (6.7%) | 218 (56.3%) |
| There is no need for screening with Pap smear in people who have received the HPV vaccine. | 79 (10.4%) | 107 (27.6%) | 201 (52.0%) |
| There is a reduced need for people who have been vaccinated against HPV to use condoms during sexual intercourse. | 93 (24.0%) | 124 (32.0%) | 170 (44.0%) |
| The price of a dose of HPV vaccine is around 1,000 TL. | 106 (27.4%) | 78 (20.2%) | 203 (52.4%) |

HPV: Human papilloma virüs, TL: Turkish liras

**Table 3. Willingness to be vaccinated**

| Variables | Yes | No | Ambivalent |
|---|---|---|---|
| I'll get the HPV vaccine | 203 (52.5%) | 43 (11.1%) | 141 (36.4%) |
| If I had a daughter. I would have her vaccinated against HPV | 216 (55.8%) | 24 (6.2%) | 147 (38.0%) |
| If I had a son. I would have him vaccinated against HPV | 206 (53.2%) | 29 (7.5%) | 152 (39.3%) |
| I buy the HPV vaccine for a fee and get it done | 118 (30.5%) | 82 (21.2%) | 187 (48.3%) |
| I will get the HPV vaccine if it is covered by social security | 225 (58.1%) | 19 (4.9%) | 143 (37.0%) |

HPV: Human papilloma virus

**Table 4. Motivators**

| Motivators | | n (%) |
|---|---|---|
| Where did you learn about the vaccine? | Social media<br>Television<br>Doctors<br>Friend<br>I didn't know about the vaccine | 202 (52.2%)<br>13 (3.3%)<br>25 (6.5%)<br>85 (22%)<br>62 (16%) |
| Which lesions does the vaccine protect against? | Condyloma (wart)<br>Cancer<br>None of them<br>All of them | 28 (7.2%)<br>72 (18.6%)<br>36 (9.3%)<br>251 (64.9%) |

cancer and HPV. In addition, the percentage of individuals aware of the cervical cancer screening programme was found to be only 25.6%. In addition, 61.2% of the participants knew that HPV infection could be sexually transmitted, and 58.1% were aware that the virus could cause condyloma. This information and studies inform us that the participants are aware that the HPV can cause visible discomfort, but they are uninformed about cervical cancer and screening programmes, which may cause a bigger health problem (5). In addition, even if the infection is not asymptomatic, those whose disease is detected or realise may cause the spread of the virus or delay in its treatment by concealing it because they are afraid of the societal judgment (3,4).

According to studies, a significant proportion of university students have low awareness of HPV infection and vaccination and limited knowledge about access to the vaccine (20). In our study, we found that only 26.6% of the participants knew about the protection offered by the HPV vaccine, and 63% did not know that there are three types of vaccines in our country. However, the rate of participants who said that vaccination should be administered to prevent HPV infection was 56.3%. A study conducted in Türkiye showed that 89% of university students wanted to be vaccinated against HPV. In our study, the rate of those who said that they would not get the vaccine even if it was included in the scope of social security was 4.9%.

Concerns about vaccine safety come to the fore in people who do not want to be vaccinated. Studies have shown that people with low levels of HPV knowledge, and those who have not received adequate health education in their educational background have a more negative view of vaccination (2,21,22). It has been shown that education programmes including accurate information about the transmission routes of HPV infection, its health effects, and the efficacy of the vaccine can increase vaccination rates (23). The importance of education in the fight against anti-vaccination is an indisputable fact. Zhang et al. (24) showed that many adolescents were willing to be vaccinated only after receiving sufficient information about the role of HPV vaccine in preventing various cancers. In our study, we found that 52.2% of the participants obtained information about the vaccine from social media, 22% from their friends, and 6.5% from doctors. Horio et al. (25) also stated in their study that brochures, videos and awareness messages for young people would increase acceptance of the vaccine. In addition, other studies have shown that the circle of friends and social media may increase the desire for HPV vaccination (26,27).

### Study Limitations

Although our study is comprehensive and conducted at a university to reveal the awareness of the young population about HPV infection and vaccination, it was incomplete in comparing gender-related approaches among the participants and in evaluating the approach to vaccination between genders and among different level of education. Again, using groups with more pronounced socioeconomic differences compared to a similar reference group may also reveal different approaches. We think that more comprehensive approaches, which can also reveal the differences between genders, could provide greater insight into educational modelling.

## Conclusion

University students have an important role in limiting HPV infection, which may be considered a public health issue. Informing young people with materials that attract young people's interest, integrating information on the subject in course curricula, and using correct education programmes can prevent the transmission routes of infection and increase vaccination rates.

### Ethics

**Ethics Committee Approval:** The study was approved by the İstanbul Esenyurt University Ethics Committee (approval number: 03, date: 05.12.2023).

**Informed Consent:** The students were first informed about the study, their consent for participation was obtained, and then the questionnaire was applied.

### Footnotes

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

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

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# Effect of Basic Point-of-Care Ultrasound Course on Physicians' Use in Clinical Practice: A Survey Study

Burcu Azapoğlu Kaymak[1], Merve Ekşioğlu[1], Özlem Dikme[2]

[1]University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye

## ABSTRACT

**Introduction:** To evaluate the impact of a basic point-of-care ultrasound (POCUS) course on physicians' clinical use of POCUS in routine medical practice.

**Methods:** This retrospective cross-sectional survey included physicians who attended one of 48 basic POCUS courses organized by the Emergency Medicine Association of Türkiye between 2019 and 2023. Among 610 physicians with available contact information, 201 completed the electronic survey, resulting in a response rate of 33%. The survey assessed participants' demographics, previous ultrasound training, and self-reported changes in POCUS usage before and after the course.

**Results:** The mean age of participants was 30.9±4.6 years, and 83.6% were emergency medicine specialists. A statistically significant increase in POCUS use was reported across all modalities following the course ($p<0.001$). The most prominent increases occurred in hepatobiliary (+58.8%), lower extremity deep vein thrombosis (+54.0%), and abdominal aorta (+50.8%) examinations. Use of POCUS for interventional procedures also rose substantially, particularly for lumbar puncture (+81.8%) and peripheral nerve blocks (+66.6%). Participants also reported enhanced diagnostic confidence, procedural competence, and integration of POCUS into decision-making.

**Conclusion:** A short, structured POCUS course led to a meaningful increase in the clinical use of ultrasound across various diagnostic and interventional domains. Despite limitations such as recall bias and lack of follow-up assessment, the findings highlight the potential of focused training to improve practice patterns. Future course designs may benefit from incorporating certification components, objective structured clinical examination-style evaluations, and opportunities for supervised practice. Follow-up or refresher training may further support skill retention and long-term integration.

**Keywords:** Point-of-care systems, ultrasonography, medical education, emergency medicine, clinical competence, surveys and questionnaires

## Introduction

Point-of-care ultrasound (POCUS) is a bedside diagnostic method increasingly integrated into clinical practice, especially in emergency medicine. It enables rapid assessment in various clinical scenarios, including chest pain, dyspnea, abdominal pain, hypotension, and during interventional procedures such as central line placement and thoracentesis (1-5). However, as an operator-dependent modality, its accuracy hinges on the user's technical and interpretative competence.

While POCUS has been incorporated into emergency medicine residency training in many countries, standardized training curricula for other specialties remain limited and heterogeneous (6-8). Structured educational programs based on established guidelines have demonstrated improvements in diagnostic performance and user confidence (9-11). However, there remains a gap in the literature regarding the long-term impact of short-duration POCUS courses, particularly in non-standardized training settings (12).

This study aims to evaluate the effect of a basic POCUS course on the clinical ultrasound usage patterns of physicians. The primary objective is to measure the change in POCUS use after the course, while the secondary objective is to identify which ultrasound applications were most frequently adopted into practice.

**Address for Correspondence:** Burcu Azapoğlu Kaymak MD, University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye
**E-mail:** burcuazapkaymak@gmail.com **ORCID ID:** orcid.org/0000-0001-7517-8637

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## Methods

### Study Design and Population

This study was designed as a retrospective cross-sectional survey. The target population consisted of 1,324 physicians who had participated in one of 48 basic POCUS courses organized by the Ultrasound Section of the Emergency Medicine Association of Türkiye between 2019 and 2023. Despite missing or outdated contact information, 610 physicians could be reached, and 201 of them completed the survey (response rate: 33%). To evaluate the sustained impact of the training, the survey was administered at least six months after participants had completed the POCUS course.

### Survey Instrument

A 28-item electronic survey was used to collect data. It included questions on demographic characteristics, specialty, years of experience, previous ultrasound training, and availability of ultrasound devices in the workplace. Physicians retrospectively evaluated their POCUS use before and after the course, including frequency and indication of use. The survey included both multiple-choice and 5-point Likert scale items, assessing perceived changes in diagnostic confidence, procedural competence, and integration of POCUS into clinical decision-making.

### POCUS Course Content

The basic POCUS course consisted of a combination of theoretical and practical sessions, delivered over a two-day format. The curriculum included ultrasound physics and knobology, Extended Focused Assessment with Sonography for Trauma (E-FAST), hepatobiliary, urinary, and genital systems, abdominal aorta, inferior vena cava, echocardiography, lower extremity deep vein thrombosis (DVT), and ultrasound-guided procedures such as vascular access and lumbar puncture. Hands-on training was conducted under supervision, with participants practicing image acquisition and interpretation on live standardized patients. Interventional techniques were practiced on gelatin-based handmade phantom models to simulate vascular and lumbar procedures.

### Statistical Analysis

Descriptive statistics were used to summarize participant characteristics. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. McNemar and McNemar-Bowker tests were used to compare pre- and post-course changes in paired categorical variables. A p-value of $<0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

### Ethical Considerations

The study was approved by the University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023/19, date: 12.10.2023), and conducted in accordance with the principles of the Declaration of Helsinki (2013 revision). Informed consent was obtained from all participants prior to their inclusion in the study.

## Results

The mean age of the participants was 30.9±4.6 years, and 53.7% were male. Most of the respondents were emergency medicine specialists (83.6%), followed by internal medicine physicians (6.5%) and general practitioners (3.5%). The average professional experience was 6.2±4.4 years. A total of 47.8% of the participants were working in training and research hospitals, 31.8% in university hospitals, and 14.9% in state hospitals.

Among the participants, 54.2% reported receiving ultrasound education for the first time, and 93% had access to an ultrasound device at their institutions. The most commonly available probe types were curvilinear (35.9%), linear (35.2%), and sector (27.8%) (Table 1).

As shown in Table 2, participants reported statistically significant increases in their self-reported use of POCUS, along with improvements in diagnostic confidence, equipment familiarity, and patient management after the course ($p<0.001$).

The frequency of POCUS use significantly increased across all scanning modalities post-course ($p<0.001$). The most prominent increases were noted in hepatobiliary (+58.8%), lower extremity DVT (+54.0%), and abdominal aorta (+50.8%) evaluations (Figure 1).

Similarly, POCUS usage increased in relation to various symptoms and signs, most notably in patients presenting with vaginal bleeding (+75.0%), fever (+62.0%), and abdominal pain (+52.8%) (Figure 2).

The use of POCUS also rose substantially for preliminary diagnoses, particularly for ovarian cyst rupture (+68.0%), ruptured ectopic pregnancy (+63.0%), and pyelonephritis (+60.8%) (Figure 3).

The frequency of POCUS use for interventional procedures increased after the course. The most prominent increases were observed in lumbar puncture (+81.8%), peripheral nerve blocks (+66.6%), and thoracentesis (+59.2%) (Figure 4).

## Discussion

The results of this study indicate that participation in a basic POCUS course significantly increased physicians' use of ultrasound across a wide range of clinical applications. Physicians reported greater diagnostic accuracy and faster decision-making after the training, which aligns with existing literature supporting the integration of POCUS into daily practice (12).

Only a subset of physicians responded to the survey (33%). Phillips et al. reported that response rates in survey-based studies in health professions vary widely, often falling below 40% in multicenter studies (13-15). To minimize non-response bias, we employed standardized electronic invitations and multiple reminders.

The most pronounced increase in usage was observed in hepatobiliary, lower extremity DVT, abdominal aorta, and echocardiographic examinations. These areas reflect both the content emphasized during the course and the clinical relevance of these modalities in emergency care.

Although some physicians were already familiar with E-FAST examinations before attending the course, the relatively modest increase in its post-course use can be attributed to the fact that it is already one of the most widely adopted ultrasound applications among emergency physicians (16). Instead, the course seems to have provided a greater boost in confidence and skill in more focused applications, such as DVT, and abdominal aorta scans, which are less commonly used without formal training.

**Table 1. Demographic characteristics of physicians participated in the study**

| Characteristic | Value |
|---|---|
| **Age (years), mean ± SD (range)** | 30.9±4.6 (25-55) |
| **Gender, n (%)** | |
| Female | 93 (46.3) |
| Male | 108 (53.7) |
| **Medical specialty, n (%)** | |
| Emergency medicine | 168 (83.6) |
| Internal medicine | 13 (6.5) |
| General practice | 7 (3.5) |
| General surgery | 4 (2.0) |
| Pediatrics | 4 (2.0) |
| Anesthesia and reanimation | 3 (1.5) |
| Neurology | 1 (0.5) |
| Other | 1 (0.5) |
| **Years in practice, mean ± SD** | 6.2±4.4 |
| **Institution type, n (%)** | |
| Training and research hospital | 96 (47.8) |
| University hospital | 64 (31.8) |
| State hospital | 30 (14.9) |
| City hospital | 6 (3.0) |
| Private hospital | 5 (2.5) |
| **Prior ultrasound training, n (%)** | |
| Yes | 92 (45.8) |
| No | 109 (54.2) |
| **Training year, n (%)** | |
| 2019 | 27 (13.4) |
| 2020 | 6 (3.0) |
| 2021 | 22 (10.9) |
| 2022 | 72 (35.8) |
| 2023 | 74 (36.8) |
| **USG device availability, n (%)** | |
| Yes | 187 (93.0) |
| No | 14 (7.0) |
| **Available USG probes, n (%)** | |
| Curvilinear (convex) | 190 (35.9) |
| Linear | 186 (35.2) |
| Sector (cardiac) | 147 (27.8) |
| Other | 6 (1.2) |

The results are expressed in terms of mean ± standard deviation (minimum and maximum) and n (%) values
SD: Standard deviation, USG: Ultrasonography

Previous studies similarly demonstrate the impact of structured ultrasound education. Tuvali et al. (12) showed that even a short POCUS course can have a long-term effect on clinical usage patterns. In a study by Jones et al. (17), family physicians reported increased confidence and more frequent use of POCUS in clinical care following training, although their skill retention diminished in areas they did not regularly practice. This supports the view that repeated exposure and clinical reinforcement are essential for sustaining competency.

De Carvalho et al. (18) and colleagues compared short-term training to longitudinal education and found that longer programs yielded higher frequency of use and greater self-confidence. This suggests that while short courses like the one evaluated in our study are effective for initiating ultrasound practice, longer or repeated sessions may be necessary to preserve skills and deepen clinical integration.

Our findings are also consistent with the results of Rajamani et al. (19), where very few participants were able to complete the number of supervised scans required for certification after a short course. Since the basic POCUS course evaluated here did not include a structured follow-up or hands-on assessment, skill retention likely varied among participants depending on clinical opportunities and individual motivation. Implementing supervised scan requirements and certification pathways may improve long-term outcomes and consistency in POCUS practice.

Another key observation is the significant increase in the use of POCUS for specific clinical complaints such as vaginal bleeding, fever, and abdominal pain, as well as for diagnoses like ovarian cyst rupture, ectopic pregnancy, and pyelonephritis. These patterns suggest that the course not only expanded procedural skills but also influenced diagnostic reasoning, promoting earlier use of POCUS in patient workup.

Several studies have addressed the durability of short-term POCUS training, indicating that the gains in knowledge and clinical use can be sustained for weeks to months after the intervention (20,21). In our study, the survey was conducted at least six months post-training, supporting the lasting impact of the course. Notably, POCUS use significantly increased for all interventional procedures, particularly lumbar puncture, peripheral nerve blocks, thoracentesis, and pericardiocentesis. Previous research has shown that ultrasound guidance in lumbar puncture improves first-attempt success rates and reduces complications, especially in patients with difficult anatomy (22,23). Similarly, ultrasound-guided thoracentesis and nerve blocks enhance procedural accuracy and safety (24-26). Pericardiocentesis, when performed under echocardiographic guidance, reduces complication rates by optimizing puncture site selection in time-sensitive conditions such as cardiac tamponade (27,28). These findings are consistent with our results and highlight how structured training can empower physicians to integrate ultrasound into procedural workflows safely and effectively.

| Table 2. Physicians views on their POCUS use before and after the basic POCUS course | | | |
|---|---|---|---|
| **Parameters** | **Before the course** | **After the course** | **p value*** |
| **I use POCUS in my patient management when indicated** | | | |
| Never | 44 (21.9) | 1 (0.5) | **<0.001** |
| Seldomly | 93 (46.3) | 8 (4) | |
| Occasionally | 42 (20.9) | 40 (19.9) | |
| Frequently | 16 (8) | 112 (55.7) | |
| Always | 6 (3) | 40 (19.9) | |
| **Incorporating POCUS into my patient management improves my diagnostic skills** | | | |
| I strongly disagree | 3 (1.5) | 1 (0.5) | **<0.001** |
| I disagree | 14 (7) | 0 | |
| I neither agree nor disagree | 78 (38.8) | 1 (0.5) | |
| I agree | 75 (37.3) | 62 (30.8) | |
| I strongly agree | 31 (15.4) | 137 (68.2) | |
| **I am familiar with the USG device and its technical features** | | | |
| I strongly disagree | 68 (33.8) | 1 (0.5) | **<0.001** |
| I disagree | 83 (41.3) | 1 (0.5) | |
| I neither agree nor disagree | 31 (15.4) | 12 (6) | |
| I agree | 14 (7) | 103 (51.2) | |
| I strongly agree | 5 (2.5) | 84 (41.8) | |
| **Incorporating POCUS into patient management allows for more accurate diagnoses of various disease processes** | | | |
| I strongly disagree | 7 (3.5) | 1 (0.5) | **<0.001** |
| I disagree | 11 (5.5) | 0 | |
| I neither agree nor disagree | 66 (32.8) | 1 (0.5) | |
| I agree | 92 (45.8) | 66 (32.8) | |
| I strongly agree | 25 (12.4) | 133 (66.2) | |
| **Incorporating POCUS into my patient management allows me to make faster diagnoses of various disease processes** | | | |
| I strongly disagree | 7 (3.5) | 1 (0.5) | **<0.001** |
| I disagree | 5 (2.5) | 0 | |
| I neither agree nor disagree | 63 (31.3) | 0 | |
| I agree | 76 (37.8) | 74 (36.8) | |
| I strongly agree | 50 (24.9) | 126 (62.7) | |
| **Incorporating POCUS into the patient management improves the follow-up skills** | | | |
| I strongly disagree | 5 (2.5) | 1 (0.5) | **<0.001** |
| I disagree | 12 (6) | 0 | |
| I neither agree nor disagree | 48 (23.9) | 3 (1.5) | |
| I agree | 108 (53.7) | 69 (34.3) | |
| I strongly agree | 28 (13.9) | 128 (63.7) | |
| **Incorporating POCUS into my patient management improves my ability to choose appropriate treatments** | | | |
| I strongly disagree | 5 (2.5) | 1 (0.5) | **<0.001** |
| I disagree | 8 (4) | 0 | |
| I neither agree nor disagree | 71 (35.3) | 4 (2) | |
| I agree | 86 (42.8) | 74 (36.8) | |
| I strongly agree | 31 (15.4) | 122 (60.7) | |

**Table 2. Continued**

| Parameters | Before the course | After the course | p value* |
|---|---|---|---|
| **Incorporating POCUS into my patient management enables me to differentiate medical emergencies** | | | |
| I strongly disagree | 6 (3) | 2 (1) | **<0.001** |
| I disagree | 4 (2) | 0 | |
| I neither agree nor disagree | 63 (31.3) | 1 (0.5) | |
| I agree | 62 (30.8) | 60 (29.9) | |
| I strongly agree | 66 (32.8) | 138 (68.7) | |
| **Incorporating POCUS into clinical patient management reduces patient morbidity** | | | |
| I strongly disagree | 4 (2) | 1 (0.5) | **<0.001** |
| I disagree | 8 (4) | 1 (0.5) | |
| I neither agree nor disagree | 93 (46.3) | 15 (7.5) | |
| I agree | 69 (34.3) | 75 (37.3) | |
| I strongly agree | 27 (13.4) | 109 (54.2) | |
| **Incorporating POCUS in my patient management improves the quality of patient care** | | | |
| I strongly disagree | 3 (1.5) | 1 (0.5) | **<0.001** |
| I disagree | 13 (6.5) | 3 (1.5) | |
| I neither agree nor disagree | 68 (33.8) | 7 (3.5) | |
| I agree | 73 (36.3) | 58 (28.9) | |
| I strongly agree | 44 (21.9) | 132 (65.7) | |
| **Incorporating POCUS into patient management reduces the length of stay in the clinic** | | | |
| I strongly disagree | 4 (2) | 3 (1.5) | **<0.001** |
| I disagree | 36 (17.9) | 9 (4.5) | |
| I neither agree nor disagree | 89 (44.3) | 39 (19.4) | |
| I agree | 50 (24.9) | 61 (30.3) | |
| I strongly agree | 22 (10.9) | 89 (44.3) | |
| **Incorporating POCUS into my patient management increases patient satisfaction** | | | |
| I strongly disagree | 10 (5) | 2 (1) | **<0.001** |
| I disagree | 14 (7) | 5 (2.5) | |
| I neither agree nor disagree | 87 (43.3) | 30 (14.9) | |
| I agree | 56 (27.9) | 64 (31.8) | |
| I strongly agree | 34 (16.9) | 100 (49.8) | |
| **Incorporating POCUS into the patient management process increases physician satisfaction** | | | |
| I strongly disagree | 6 (3) | 1 (0.5) | **<0.001** |
| I disagree | 14 (7) | 1 (0.5) | |
| I neither agree nor disagree | 71 (35.3) | 15 (7.5) | |
| I agree | 75 (37.3) | 66 (32.8) | |
| I strongly agree | 35 (17.4) | 118 (58.7) | |
| **A POCUS course should be part of the medical education curriculum for both resident and specialist physicians** | | | |
| I strongly disagree | 0 | 0 | **<0.001** |
| I disagree | 6 (3) | 1 (0.5) | |
| I neither agree nor disagree | 40 (19.9) | 3 (1.5) | |
| I agree | 60 (29.9) | 52 (25.9) | |
| I strongly agree | 95 (47.3) | 145 (72.1) | |

Results are expressed as n (%). *: McNemar-Bowker test
Bold p-values indicate statistical significance (p≤0.05). POCUS: Point-of-care ultrasound, USG: Ultrasonografi

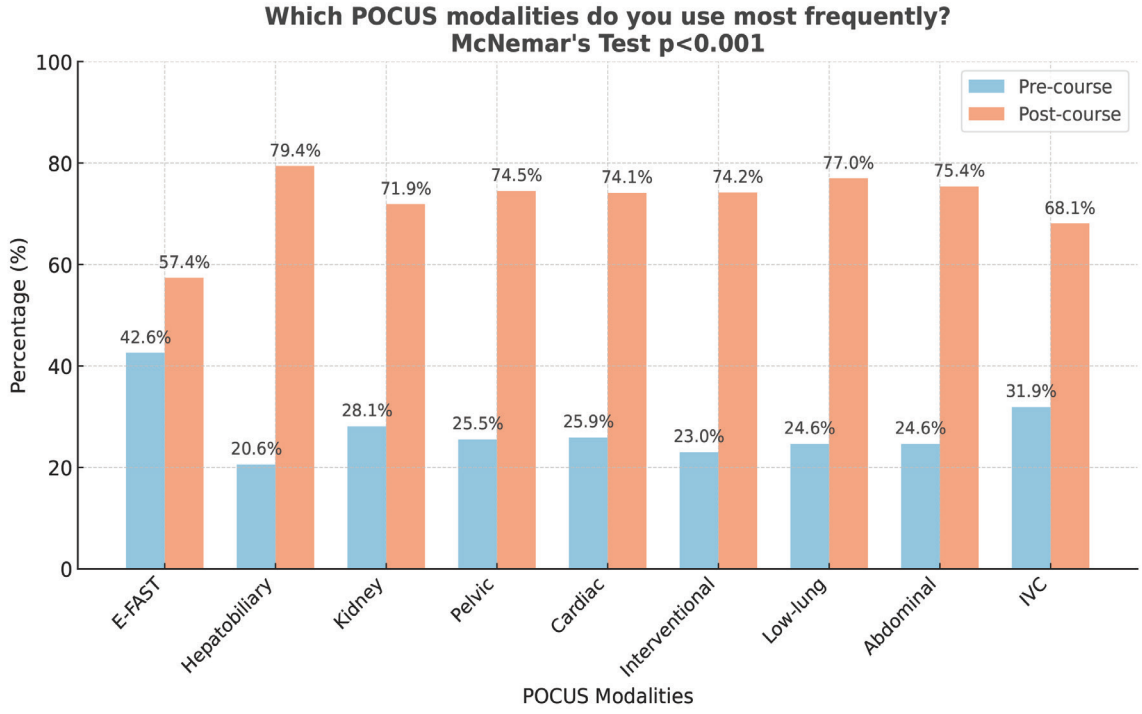



**Figure 1.** This figure demonstrates the significant increase in the use of POCUS across all modalities by physicians, after completing the basic POCUS course, highlighting the most notable changes in hepatobiliary, DVT, and abdominal aorta evaluations
POCUS: Point-of-care ultrasound, DVT: Deep vein thrombosis

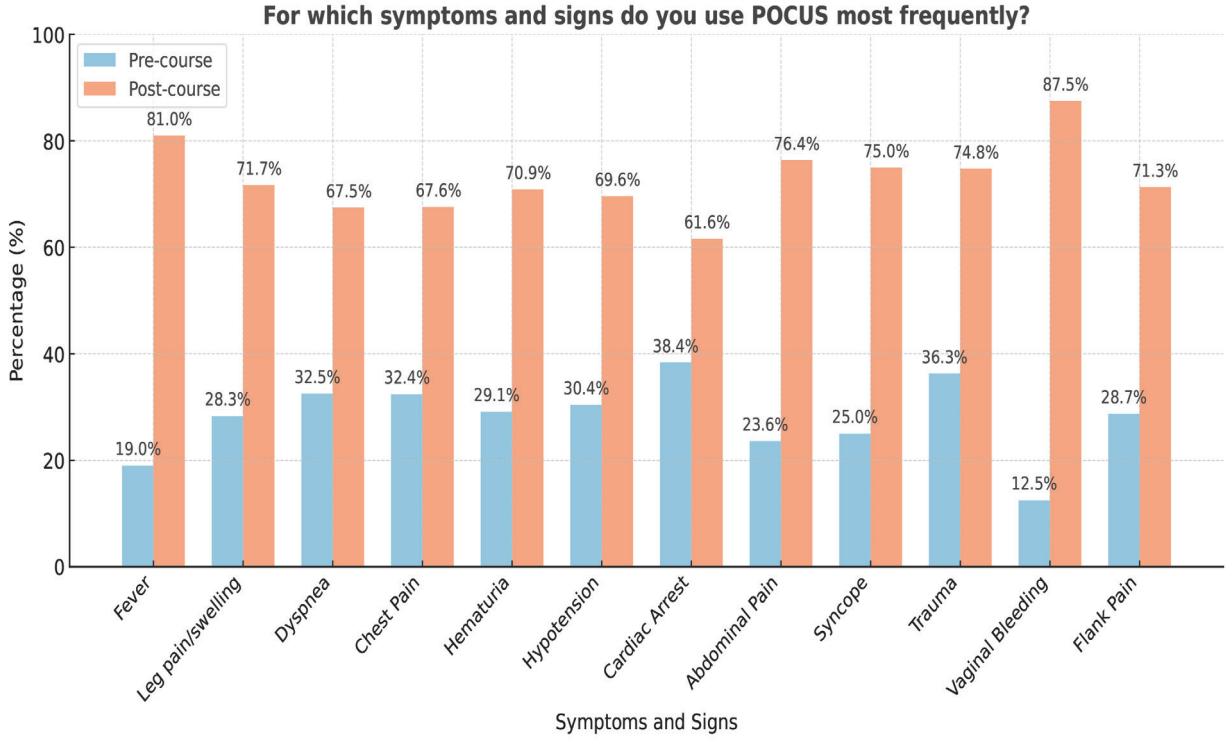



**Figure 2.** This figure illustrates the increased frequency of POCUS use for various symptoms and signs after the course, with the highest growth observed in evaluations for vaginal bleeding, fever, and abdominal pain
POCUS: Point-of-care ultrasound

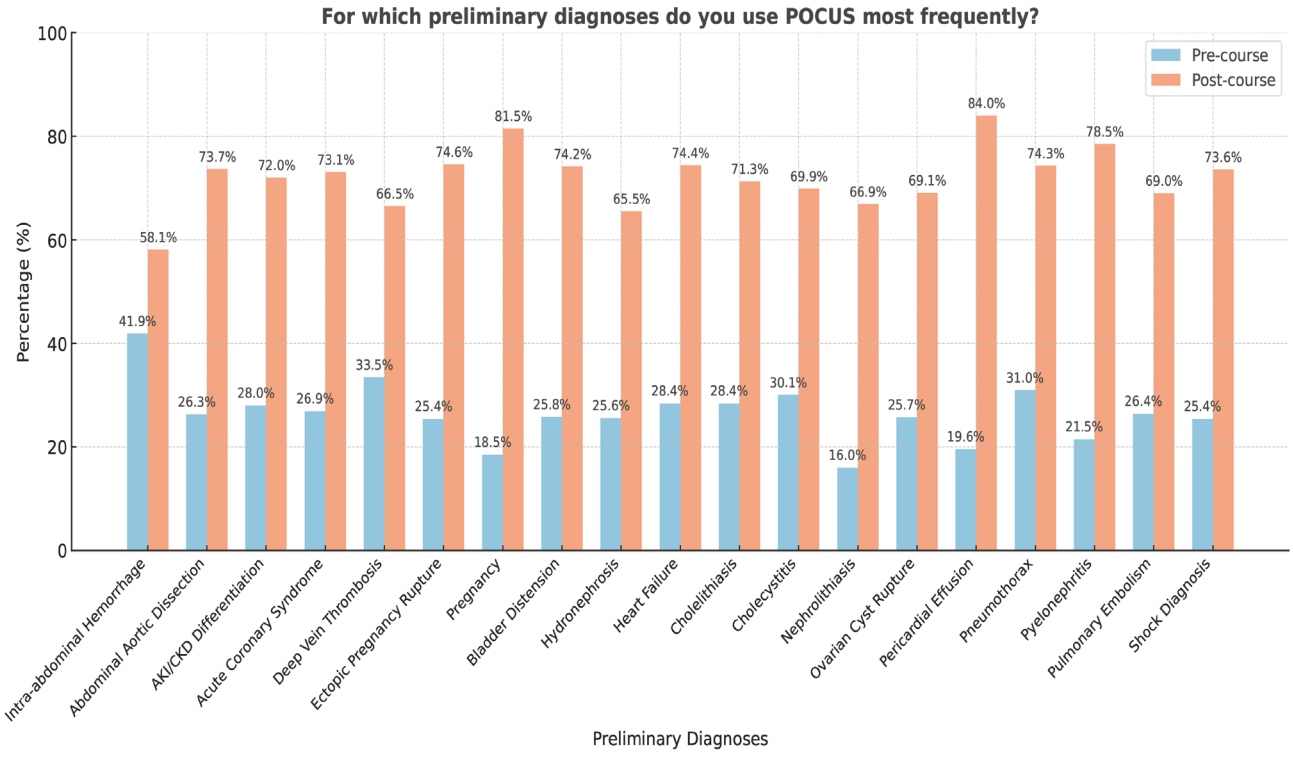



**Figure 3.** This figure presents the changes in POCUS use for preliminary diagnoses, showcasing the most significant increases for ovarian cyst rupture, ruptured ectopic pregnancy, and pyelonephritis after the course
POCUS: Point-of-care ultrasound

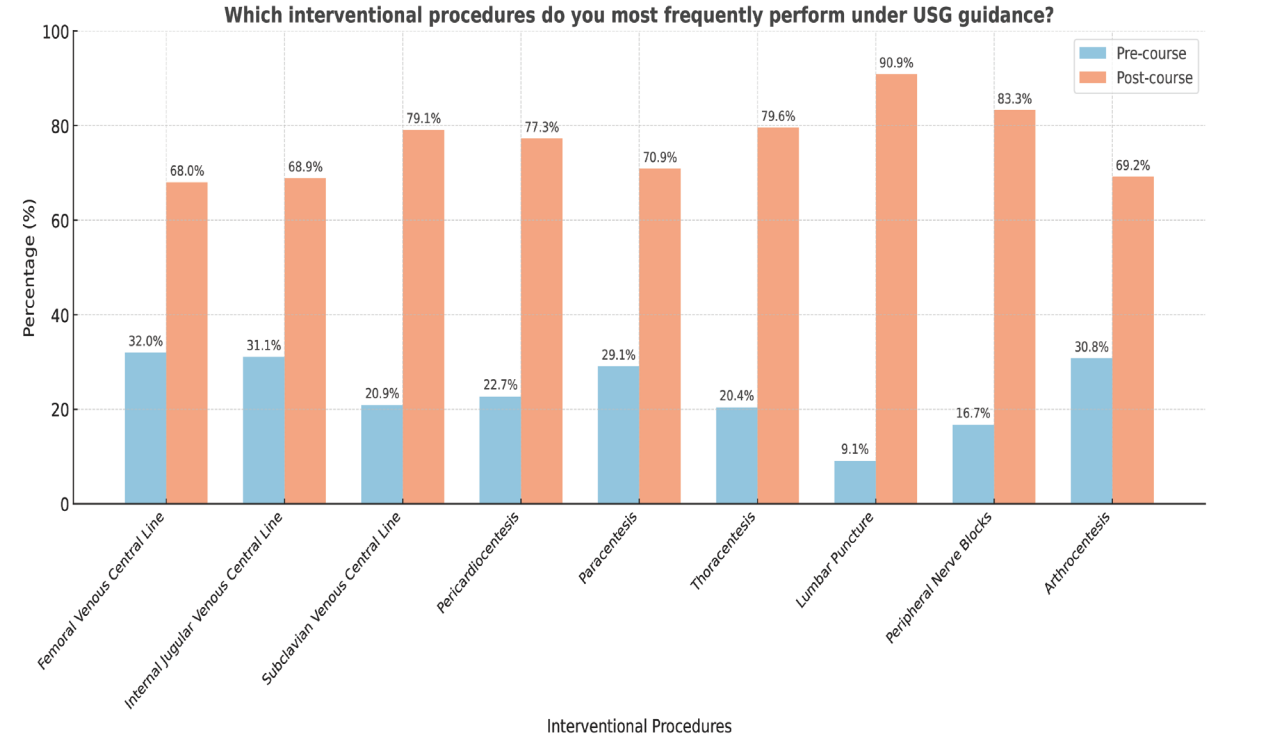



**Figure 4.** This figure highlights the substantial growth in POCUS use for interventional procedures following the course, particularly for lumbar puncture, peripheral nerve blocks, and thoracentesis
POCUS: Point-of-care ultrasound,USG: Ultrasonografi

### Study Limitations

Although the data show a clear trend toward increased ultrasound use after the course, several methodological limitations should be considered. The survey was completed by only 201 of 610 physicians who were contacted, resulting in a 33% response rate. This raises the possibility of non-response bias, as those more positively influenced by the course may have been more likely to participate. Additionally, participants were asked to retrospectively evaluate their POCUS usage prior to the course, which may have introduced recall bias. The absence of a structured follow-up assessment, supervised practice, or certification component further limits the ability to determine long-term skill retention or clinical competency. Lastly, the sample was composed predominantly of emergency physicians working in tertiary hospitals, which may limit the generalizability of the findings to other specialties and practice settings.

## Conclusion

This study demonstrates that even a short, structured POCUS course can lead to a marked increase in physicians' self-reported use of ultrasound across various diagnostic and procedural domains. While the findings suggest a positive shift in clinical behavior, further research is warranted to evaluate the long-term retention of skills and direct impact on patient outcomes. Broader implementation of standardized ultrasound training, with opportunities for hands-on practice and follow-up assessment, may enhance the integration of POCUS into clinical workflows. Future course designs may benefit from incorporating certification pathways, structured supervised practice, and practical skill evaluations such as objective structured clinical examinations. Additionally, longitudinal training formats, refresher sessions, and re-training opportunities may help reinforce skill retention and optimize long-term clinical integration.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023/19, date: 12.10.2023).

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

### Footnotes

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

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# The Relationship Between Malnutrition and Mortality in Patients Hospitalized with COVID-19

Nezihe Çiftaslan Gökşenoğlu[1], Osman Ekinci[2]

[1]Göztepe Training and Research Hospital, Clinic of Intensive Care Unit, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital, Clinic of Intesive Care Unit, İstanbul, Türkiye

## ABSTRACT

**Introduction:** Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 infection, was first reported by the Chinese Center for Disease Control and Prevention in December 2019 in Wuhan. It is known that the risk of malnutrition adversely affects several clinical outcomes, such as the length of hospitalisation and mortality, in non-COVID-19 cases. Further, if this group of patients needs to be followed up in the intensive care unit (ICU), early diagnosis and rapid intervention are recommended. The aim of our study was to determine the effect of the presence of malnutrition risk on mortality and prognosis in patients hospitalised due to COVID-19.

**Methods:** One thousand one hundred seventy-seven patients who were diagnosed with COVID-19 and hospitalised after their polyclinics and emergency applications between March 2020 and July 2020 were evaluated. The malnutrition risk of the patients was evaluated using nutritional risk screening, and patients with a score of >3 were considered at risk of malnutrition. The relationship between malnutrition risk and mortality was then evaluated among patients with COVID-19, hospitalised in the service wards and the ICU.

**Results:** One thousand one hundred seventy-seven patients were eventually evaluated retrospectively. One hundred twenty-three (10.5%) were hospitalized in the ICU on arrival, and 862 (73.2%) were inpatients in the infection clinic. In addition, 120 (10.2%) patients were followed up in the ICU because they required intensive care. Mortality was evaluated in the entire inpatient group, with the number of observed deaths being n=232. The mortality rate was the highest in the intensive care unit (n=76, 32.8%), followed by the infectious diseases service (n=71, 30.6%). When the relationship between malnutrition risk and mortality was evaluated, mortality was found to be significantly higher in the patient group with malnutrition risk ($p<0.05$). The correlation between malnutrition risk and mortality in patients followed up in the ICU was found to be higher than that in all other groups. In addition, it was observed that the mortality rate of patients found to have a risk of malnutrition at the time of admission to the ICU during follow-up was higher than that of patients in the service wards.

**Conclusion:** Malnutrition risk is an important indicator for determining the prognosis of hospitalised patients. In our study, the risk of malnutrition increased the risk of mortality and length of hospitalisation among inpatients diagnosed with COVID-19. In our study, the mortality rate among the patient group with malnutrition risk was 42%. Moreover, malnutrition risk and mortality rate were higher in patients hospitalised in the ICU. Nutrition is an integral part of the treatment for COVID-19, as in all critically ill patients. Appropriate nutrition and a strong immune system are important components alongside any medication used to treat COVID-19. Prevention, diagnosis, and treatment of malnutrition should be routinely included in the treatment of patients with COVID-19.

**Keywords:** Malnutrition, mortality, COVID-19

## Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 infection, first reported by the Chinese Center for Disease Control and Prevention in December 2019 in Wuhan, Hubei province of China. It was later declared a global pandemic by the World Health Organization on 11 March 2020 (1).

Numerous studies have been published highlighting the potential risk and prognostic factors for the development and severity of COVID-19. The presence of comorbidities such as cardiovascular diseases and chronic obstructive pulmonary disease, along with age, has been identified as important determinants of mortality (2).

**Address for Correspondence:** Nezihe Çiftaslan Gökşenoğlu MD, Göztepe Training and Research Hospital, Clinic of Intensive Care Unit, İstanbul, Türkiye
**E-mail:** neziheciftaslan@gmail.com **ORCID ID:** orcid.org/0000-0003-3860-5905

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However, little is known about the impact of nutrition on the prognosis and disease course of COVID-19.

Studies have reported that malnutrition risk is associated with worse disease course, and outcome, and greater susceptibility to infection.

It is known that malnutrition risk adversely affects several clinical outcomes, such as the length of hospitalisation and mortality, in non-COVID-19 cases (3,4). Furthermore, should this group of patients need to be followed up in the intensive care unit (ICU), early diagnosis and rapid intervention are recommended (5).

Nutritional risk screening-2002 (NRS-2002) is one of the recommended tests to assess malnutrition among inpatients (6).

By performing nutritional screening, further declines in nutritional status during hospitalisation can be prevented, and clinical outcomes improved.

The aim of our study was to determine the effect of the presence of malnutrition risk on mortality and prognosis in patients hospitalised due to COVID-19.

## Methods

This study evaluated the risk of malnutrition using NRS-2002 scores in patients hospitalised in service wards and ICUs due to COVID-19. The study was approved by the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: HNEAH-KAEK 2021/121, date: 24.05.2021). In our hospital, 1,177 patients who were hospitalised with the diagnosis of COVID-19, after their polyclinic and emergency visits between March 2020 and July 2020 were evaluated. Patients who were hospitalised in the 21-bed ICU, infectious diseases clinic, internal medicine service, general surgery service, and nephrology clinic were included in the study.

For the diagnosis of COVID-19, the following were used as the diagnostic criteria: positive polymerase chain reaction (PCR) test for patients' samples obtained through nasal swabs; presence of COVID-19-specific findings on chest computed tomography (CT) or negative PCR and positive CT; presence of close contact with patients with a definitive diagnosis of COVID-19; symptoms such as fever, dry cough, anosmia, diarrhoea, myalgia, hypoxic respiratory failure, and lymphocytopenia; and elevated levels of D-dimer, ferritin, fibrinogen, and C-reactive protein (along with normal levels of procalcitonin).

Patients who needed inpatient treatment were hospitalised in accordance with the algorithm and criteria established by the Ministry of Health. The treatments recommended by the Ministry of Health were initiated at appropriate doses for the patients. Patients hospitalized in the ICU received ventilator support and were monitored according to their needs.

The patient records were reviewed retrospectively, and the data were evaluated. The patients' age, sex, comorbidities, and service under which they were treated were recorded.

The lengths of hospitalisations in the service wards and in the ICU were recorded. The intensive care needs of the patients in the service follow-up were evaluated, and the patients who were transferred from the service wards to the ICU were recorded. Inpatient mortality of patients hospitalised in the service wards and the ICU due to COVID-19 was evaluated.

The malnutrition risk of the patients was evaluated using NRS-2002, and patients with a score of >3 were considered to have the risk of malnutrition.

### NRS-2002

A prescreening test was first performed, wherein the individual was asked whether their body mass index was <20.5 kg/m$^2$, whether they had lost weight in the last 3 months, whether there was a decrease in food intake in the last week, and whether the patient's condition was severe. If the answer to any of these questions was yes, the main screening was performed.

The NRS-2002 scoring system comprises two parameters: "nutritional status" and "severity of the underlying disease". It provides scores ranging from 1-3 for the individual's condition: "nourished", "mild malnutrition", "moderate malnutrition" or "severe malnutrition". In patients aged >70 years, 1 point was added to the total score. Those with a total score of ≥3 were assumed to be at risk of malnutrition, and a nutritional evaluation was recommended for these patients.

The risk of malnutrition was evaluated and recorded within the first 48 hours after the patient's hospitalisation.

NRS-2002 assessments were performed by an intensive care specialist, service physicians, three dietitians, and two nurses in the nutritional support team.

The relationship between malnutrition risk and mortality was then evaluated among patients with COVID-19 hospitalised in the service wards and the ICU.

### Statistical Analysis

The IBM SPSS Statistics 25 program was used for evaluating the data on sex, age, polyclinic care, and length of hospitalisation of 1,177 patients with COVID-19. The crosstab analysis was employed for assessing malnutrition and mortality status. Chi-squared and Pearson's correlation analyses were performed to analyze the percentage and frequency distributions of the categorical variables. The age and length of hospitalisation variables were collected metrically and then converted into categorical variables based on standard deviation values.

## Results

The flowchart of the study patients is summarised in Figure 1. During the study, 1,199 patients hospitalised in the inpatient service wards and ICUs at our hospital, between March 2020 and July 2020, were evaluated. Among these, 22 were referred to an external centre for different reasons, during their follow-up, and the data of 1,177 patients were eventually evaluated retrospectively.

The female/male ratio was 541/636 (46%/54%), and mean age of the included patients was 61.52±17.44 (range, 16-97) years (Table 1).

Chronic diseases included hypertension, chronic obstructive pulmonary disease, coronary artery disease and chronic kidney disease.

Among the included patients, 123 (10.5%) were hospitalised in the ICU on arrival, and 862 (73.2%) were in the infection clinic as inpatients. The remaining patients were followed up under the internal medicine, general surgery, and nephrology services. In addition, 120 (10.2%)

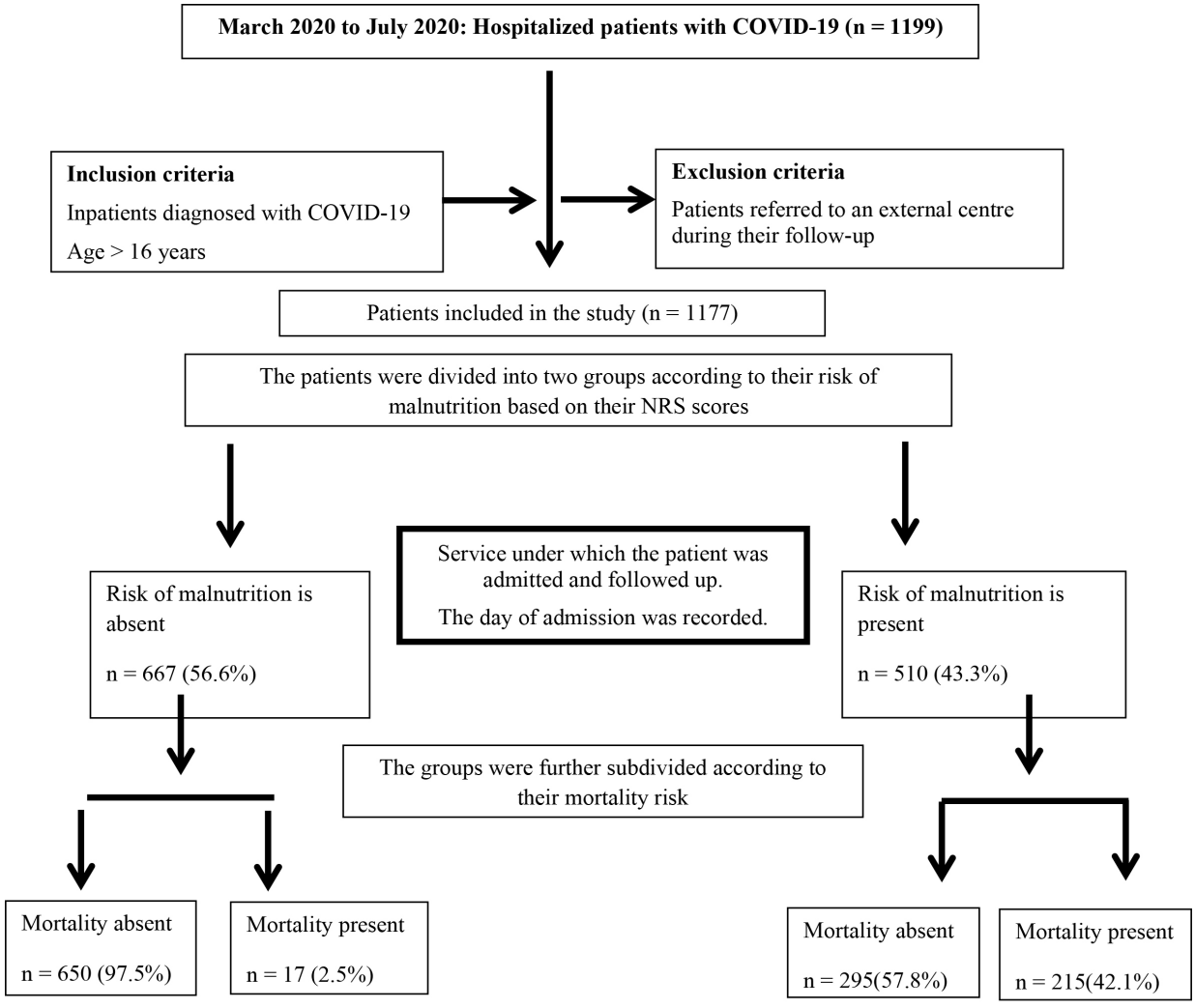



**Figure 1.** Flow chart of the study
COVID-19: Coronavirus disease-2019, NRS: Nutritional risk screening

**Table 1. The risk of malnutrition based on the characteristics of the patients**

| | Total | Risk of malnutrition is absent | Risk of malnutrition is present |
|---|---|---|---|
| Sex, n (%) (female%/male%) | 541/636 (46%/4%) | 295/372 (44.2%/55.8%) | 246/264 (48.2%/51.8%) |
| Age, years | 61.52±17.44 (16-97) | 61±5.3 | 60±2.6 |
| Comorbidities, n (%) | 752 | 462 (61%) | 290 (39%) |
| Length of hospitalisation, days (mean ± SD) | 8.28±7.51 | 7.65 (±4.9) | 9.11 (±9.8) |
| Follow-ups in the service wards, n (%) | 934 | 641 (68.6%) | 293 (31.3%) |
| Follow-ups in the intensive care unit, n (%) | 243 | 26 (10.6%) | 217 (89.3%) |

SD: Standard deviation

patients were followed up in the ICU due to the need for intensive care during service follow-ups.

The demographic characteristics of the patients are summarised in Table 1.

Table 2 shows the total number of patients with malnutrition risk among the hospitalised patients, and the number of patients with malnutrition risk divided by the service wards to which they were admitted.

Mortality was evaluated in the entire inpatient group and was observed to be n=232. The mortality rate was the highest in the ICU (n=76, 32.8%), followed by the infectious diseases service (n=71, 30.6%).

When the relationship between malnutrition risk and mortality was evaluated, mortality was found to be significantly higher in the patient group with malnutrition risk (Table 3) ($p<0.05$).

The correlation between malnutrition risk and mortality in patients followed up in the ICU was found to be higher than that in all other groups. In addition, it was observed that the mortality rate was higher for patients who were at risk of malnutrition during follow-up. This observation was particularly noted when they were admitted to the ICU, compared to the patients in the service wards (Table 4).

Analysis was performed on the effect sizes derived from the crosstab results showing the distribution of malnutrition and mortality status. Since the relevant analysis was based on crosstab results, Cramer's V value was taken into account for the effect size. Accordingly, it has a high effect size. size (Cramer's V value: 0.493).

## Discussion

Malnutrition risk is an important indicator for determining the prognosis of hospitalised patients. In our study, it was observed that malnutrition increased mortality risk, and length of hospitalisation among inpatients diagnosed with COVID-19.

COVID-19 is most commonly followed by pneumonia in hospitalised patients. One of the factors that negatively affects the prognosis for community-based pneumonia is nutritional deficiency. An appropriate nutritional status is important for maintaining an adequate immune response against infections (7-10).

A study has reported that malnutrition was found to be one of the factors affecting mortality in cases of viral infections caused by influenza A and B, which are respiratory tract-associated viruses (11).

**Table 2. Total number of patients with malnutrition risk and number of patients with malnutrition risk according to the service wards they were admitted to**

| | Those with malnutrition risk, n (%) | Those without malnutrition risk, n (%) | Total |
|---|---|---|---|
| Infectious diseases service | 257 (21.8%) | 605 (51.4%) | 862 |
| Intensive care unit | 123 (10.5%) | 0 | 123 |
| Patients transferred from the service ward to the intensive care unit | 94 (18%) | 26 (3%) | 120 |
| Internal medicine service | 18 (1.5%) | 26 (2.2%) | 44 |
| Other | 18 (3%) | 10 (1%) | 148 |
| Total | 510 (43.3%) | 667 (56.7%) | 1,177 |

Other: General surgery service and nephrology service

**Table 3. Relationship between malnutrition and mortality**

| | Risk of malnutrition is absent n (%) | Risk of malnutrition is present n (%) | Total | p value |
|---|---|---|---|---|
| No mortality | n=650 (68.8%) | n=295 (31.2%) | 945 | |
| Mortality | n=17 (7.3%) | n=215 (92.7%) | 232 | |
| Total | 667 | 510 | 1,177 | <0.005 |

**Table 4. Mortality of patients at risk of malnutrition depending on the service wards they were admitted to**

| Those at risk of malnutrition | Mortality is absent n (%) | Mortality is present n (%) | Total |
|---|---|---|---|
| Infectious diseases service | 193 (65.4%) | 64 (29.8%) | 257 |
| Intensive care unit | 47 (15.9%) | 76 (35.3) | 123 |
| Patients transferred from the service ward to the intensive care unit | 25 (8.5%) | 69 (32.1%) | 94 |
| Other | 30 (10.2%) | 6 (2.8%) | 36 |
| Total | 295 (58%) | 215 (42%) | 510 |

Other: Internal medicine service, nephrology service and general surgery service

In another study evaluating viral pandemics in the past years, regions with high malnutrition levels were found to have the highest mortality rates (12).

In the study by Özışık et al. (13), the risk factors of mortality for respiratory tract infections caused by influenza-like viruses were investigated. It was found that the risk of malnutrition was associated with poor clinical outcomes in the patient group that required hospitalisation.

An increase in body temperature leads to a 10%-15% increase in energy consumption per degree (°C). The increase in energy consumption during the disease course is also a result of the increase in sympathetic activity (14). However, in patients with COVID-19, symptoms such as fever (88.7%), cough (>80%), respiratory distress (18.6%), along with gastrointestinal (GIS) symptoms like diarrhoea (3.8%) and nausea (5.0%) may be observed. While fever, chills, tachypnoea, increased work of breathing, hypoxia, inflammation and cytokine storm increase energy consumption in patients with COVID-19, GIS problems impair intake and facilitate malnutrition (15,16).

As a result, resistance to infections decreases and disease burden increases (17).

Our study observed that the risk of malnutrition prolonged the length of hospitalisation and increased mortality due to COVID-19.

In a meta-analysis published by Abate et al. (18) in 2021, the prevalence of malnutrition among hospitalised patients was found to be 49.11% (11.57%-88.39%).

This meta-analysis included 14 studies and 4187 inpatients with COVID-19 (19).

The risk of malnutrition among inpatients was found to be 43.3%.

The meta-analysis also showed that the mortality rate among hospitalised patients with COVID-19 was 10 times higher than that among those who were well-nourished (18). The mortality rate among malnourished patients with COVID-19 in the included studies ranged from 10% to 59.09%.

In the study conducted by Zhao et al. (20) on 413 severe and critical patients, in which the risk of malnutrition was evaluated based on the NRS-2002 score, the mortality rate and length of hospitalisation were found to be high in patients with malnutrition.

In our study, the mortality rate among the patient group with malnutrition risk was 42%. Further, malnutrition risk and mortality rate were higher in patients hospitalised in the ICU.

In our study, malnutrition risk was determined using NRS-2002. Studies have shown that NRS-2002, mini nutritional assessment-long/short, and nutritional risk index are better than other tests in detecting malnutrition in hospitalised patients (21).

ESPEN recommends the use of NRS-2002 in hospitalised patients. The values reported in the literature of its sensitivity, specificity and positive predictive value are around 62, 93 and 85%, respectively (22).

Studies have shown that biomarkers are poor indicators of nutritional status, malnutrition risk calculated based on albumin levels is low because prealbumin levels can be affected by critical illness, infection, liver disease, and kidney disease (18,23).

Considerable uncertainty remains about nutritional management in COVID-19, with recommendations based on the guidelines of the European Society for Clinical Nutrition and Metabolism and the American Society for Parenteral and Enteral Nutrition, expert opinions, and clinical experience.

Compared with other studies in the literature, our study was conducted with a higher number of patients, and significant results were obtained when evaluating the relationship between malnutrition risk and mortality.

Although nutritional status has not been adequately studied in patients with COVID-19, nutritional disorders appear to be associated with worse disease course and outcome, possibly due to greater susceptibility to infection.

Nutrition is an integral part of the treatment for COVID-19, as in all critically ill patients. Appropriate nutrition and a strong immune system are as important as any other intervention used to treat COVID-19. The prevention, diagnosis, and treatment of malnutrition should be routinely considered in the care of patients with COVID-19.

### Study Limitations

Malnutrition was evaluated with the NRS score in hospitalized patients diagnosed with COVID-19, and different measurement techniques could also be added to diagnose malnutrition. Since this constitutes a critical patient group requiring isolation, methods such as anthropometric measurements were not used.

## Conclusion

The risk of malnutrition in patients with COVID-19 who receive inpatient treatment may have a negative effect on their prognosis. malnutrition increased the length of hospitalisation. Hence, determining the risk of malnutrition and supporting a patient's nutrition during inpatient treatment should be integral to the treatment.

### Ethics

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (approval number: HNEAH-KAEK 2021/121, date: 24.05.2021).

**Informed Consent:** Retrospective study.

### Footnotes

**Authorship Contributions:** Concept - N.Ç.G., O.E.; Design - N.Ç.G., O.E.; Data Collection or Processing - O.E.; Analysis or Interpretation - N.Ç.G., O.E.; Literature Search - N.Ç.G.; Writing - N.Ç.G., O.E.

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

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