E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 26 • ISSUE 4 • November 2025

Original Articles

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İstanbul MEDICAL JOURNAL

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Mehmet TOPTAŞ

Department of Anesthesiology and Reanimation, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, İstanbul, Türkiye

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Publisher Contact
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Phone: +90 (530) 177 30 97 / +90 (539) 307 32 03
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Publication Date: November 2025
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published four times in a year.

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Mehmet Salih GÜREL
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Nagehan Didem SARI
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Mustafa YILDIRIM
Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, İstanbul, Türkiye

Naim MAHROUM
Department of Infectious Diseases and Clinical Microbiology, Tel Aviv University Faculty of Medicine, Tel Aviv, İsrail

Physical Medicine and Rehabilitation

Ebru AYTEKİN
Department of Physical Medicine and Rehabilitation, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, İstanbul, Türkiye

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Department of Physical Therapy and Rehabilitation, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye

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Department of General Surgery, University of Health Sciences Türkiye, Başakşehir Çam and Sakura Training and Research Hospital, İstanbul, Türkiye

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Ufuk Oğuz İDİZ
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Hasan ÖKMEN
Department of General Medicine, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, İstanbul, Türkiye

Chest Diseases

Erdoğan ÇETİNKAYA
Department of Chest Diseases, University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

Seda TURAL ÖNÜR
Department of Chest Diseases, University of Health Sciences Türkiye, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

Sedat ALTIN
Department of Chest Diseases, University of Health Sciences Türkiye, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Türkiye

Alexandru CORLATEANU
Department of Chest Diseases, State University of Medicine and Pharmacy, Moldova

Chest Surgery

Kemal KARAPINAR
Department of Chest Surgery, University of Health Sciences Türkiye, İstanbul Yedikule Pulmonary Diseases and Thoracic Surgery Training and Research Hospital, İstanbul, Türkiye

Levent CANSEVER
Department of Chest Surgery, University of Health Sciences Türkiye, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Türkiye

Eye Diseases

Özen AYRANCI
Department of Eye Diseases, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, İstanbul, Türkiye

Yusuf YILDIRIM
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Owner: Istanbul Training and Research Hospital

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İstanbul Med J 2025; 26(4): 259-64
DOI: 10.4274/imj.galenos.2025.33667

Comparative Evaluation of Treadmill-Based Risk Scores: Insights into Coronary Risk Stratification and Clinical Utility

Hakan Gökalp Uzun, Burcu Uludağ Artun

University of Health Sciences Türkiye, İzmir City Hospital, Clinic of Cardiology, İzmir, Türkiye

ABSTRACT

Introduction: Treadmill stress electrocardiogram (ECG) testing is widely used for coronary artery disease (CAD) assessment, but its accuracy is limited when based solely on ST-segment changes and exercise capacity. Several treadmill-based risk scores-Duke Treadmill score (DTS), Morise score (MS), Cleveland clinic prognostic score (CCPS), FIT Treadmill score (FITTS), and Rancho Bernardo score (RBS)-aim to improve risk stratification, but their comparative effectiveness remains unclear. This study evaluates their correlation and clinical applicability.

Methods: This cross-sectional study analyzed 136 patients undergoing treadmill stress testing at a cardiology outpatient clinic. Patients with contraindications or significant baseline ECG abnormalities were excluded. Demographic, clinical, and exercise test parameters were recorded. Risk scores were calculated using predefined equations, and Spearman's rank correlation was used to assess relationships among scores.

Results: The cohort had a mean age of 46±13 years, with 43.4% women. Cardiovascular risk factors were common, including hyperlipidemia (24.3%), diabetes (11.8%), hypertension (25%), and smoking (43.4%). The categorical agreement was moderate between DTS and MS (κ=0.42) between CCPS and MS (κ=0.37), fair between MS and FITTS, DTS and RBS, and FITTS and CCPS (κ=0.23-0.32), and only slight for the remaining pairs (κ=0.07-0.12). Risk categorization varied significantly, with DTS and MS, predominantly classifying patients as low-risk, while FITTS and RBS provided a broader risk distribution.

Conclusion: Treadmill risk scores vary in the context of CAD risk classification. DTS is useful for identifying high-risk patients, while FITTS and CCPS may better assess lower-risk individuals. Combining scores may enhance risk stratification. Further research with long-term outcomes is needed.

Keywords: Treadmill stress testing, coronary artery disease, risk scoring models, Duke Treadmill score, Morise score, Cleveland clinic prognostic score, exercise capacity, risk stratification

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in the world (1). A timely diagnosis may prevent irreversible myocardial damage. Treadmill stress electrocardiogram (ECG) testing has been used as a primary tool for decades for the detection of CAD. The presence and/or degree of ST depression, along with the exercise intensity achieved during testing, provide some prognostic value; however, these variables have limited accuracy and precision. To enhance diagnostic and prognostic strength, various scoring models have been developed that incorporate additional variables beyond treadmill-based factors, including clinical and demographic risk factors.

Despite the proliferation of treadmillderived algorithms, only a handful of studies have juxtaposed these scores directly and most were performed more than two decades ago, enrolled highly selected male cohorts, or used heterogeneous endpoints such as angiographic stenosis versus clinical events (2-4). These observations underscore the importance of understanding how interchangeable traditional and contemporary treadmill scores, when applied to today's mixed-gender, risk-factor-rich outpatient population, are. Addressing this gap may help clinicians choose the most appropriate score for specific patient phenotypes and optimize downstream testing.

The optimal risk scoring scheme should be inclusive, incorporate all potential risk factors, and be easy to implement at the point of clinical care. Our study, based on a patient sample presenting to the cardiology outpatient clinic, aimed to compare the prominent treadmill score models and to investigate correlations as well as to illuminate their strengths and weaknesses.

Address for Correspondence: Hakan Gökalp Uzun MD, University of Health Sciences Türkiye, İzmir City Hospital, Clinic of Cardiology, İzmir, Türkiye
E-mail: hakangokalpuzun@gmail.com **ORCID ID:** orcid.org/0000-0003-4194-0579

Cite this article as: Uzun HG, Uludağ Artun B. Comparative evaluation of treadmill-based risk scores: insights into coronary risk stratification and clinical utility. İstanbul Med J. 2025; 26(4): 259-64

Received: 17.03.2025
Accepted: 07.08.2025
Publication Date: 12.11.2025

Methods

Study Population and Design

This is a descriptive, cross-sectional study designed to compare five different treadmill scores and explore how these scores vary based on the variables used in their calculation. The study cohort consisted of patients who underwent exercise ECG testing in our cardiology outpatient clinic with an indication for the diagnosis of coronary heart disease. Indications were selected at the discretion of the treating physician according to standard protocols in our outpatient clinic, following the latest guidelines on the subject. All consecutive applicants who were willing to comply with all study requirements were included. Accordingly, patients with any of the absolute contraindications for exercise stress test (EST) according to the guidelines were excluded (5). Furthermore, participants with baseline electrocardiographic abnormalities that might interfere with the assessment of ST-segment deviations, such as left bundle branch block or paced rhythm, were excluded. Patients underwent a comprehensive cardiac evaluation, including transthoracic echocardiography.

We collected demographic and clinical data including comorbidities and risk factors for coronary heart disease.

Test Procedure

EST was done using an integrated digital treadmill ECG system (GE T2100-ST, GE Healthcare, Chicago, Illinois, USA). Testing was performed following established guidelines (5). ECG recordings were obtained with a 12-lead system (Mason-Likar) with electrodes placed in modified positions (6).

Patients were instructed to continue their daily medications, including beta-blockers, as withholding does not appear to affect exercise performance (7).

The test was considered appropriate for the assessment if the patient reached 85% of their age-predicted maximum (max.) heart rate (APMHR) or achieved >7 metabolic equivalents (METs) of workload. APMHR was estimated using the equation "220-age" (8). The test was deemed "non-diagnostic" if neither of the two sufficiency criteria was fulfilled and the patient had no abnormal ECG changes.

Horizontal/downsloping ST-depression of at least 1 mm was considered abnormal (5). ST-segment depressions that were present before the exercise were subtracted from the peak depressions. The Treadmill scores (see Tables 1 and 2 for a summary).

Duke Treadmill Score (9)

The Duke Treadmill score (DTS) is the most widely used and cited exercise score since its invention in 1987. Its formula consists of three variables: total exercise time, largest ST-segment deviation in any lead measured in millimeters (except in lead aVR), and angina index (1= non-limiting angina and 2= exercise-limiting angina). It lacks some key variables such as age and heart rate. Total scores of ≥+5, -10 to +4, and <-10 correspond to low, intermediate, and high-risk levels, respectively, with associated 5-year survival rates of 99%, 95%, and 79%.

The equation is as follows: score = exercise time - [(5× ST-depression) + (4× angina index)].

Morise Score (Prognostic Exercise Test Scores for Men and Women) (10)

Developed in 2003 by Morise et al. (10), this externally validated tool differs from DTS mainly by separating scores by gender. The variables common to both genders are maximal heart rate, exercise ST-segment depression, age, angina history, diabetes, and the presence of exercise test-induced angina. Outside these shared domains, women are questioned about smoking and estrogen status, while men are asked

Table 1. Summary of Treadmill risk scores

Score	Year	Key variables	Risk categories	Survival estimates
Duke Treadmill score (9)	1987	- Total exercise time - ST-segment deviation (mm) - Angina index	• ≥+5: low-risk • -10 to +4: intermediate-risk • ≤-10: high-risk	5-year survival: 99% (low) 95% (intermediate) 79% (high)
Morise score (10)	2003	- Maximal heart rate - Exercise ST-segment depression - Age - Angina history - Diabetes - Gender-specific (smoking, estrogen for women; hypercholesterolemia for men)	• <40: low probability • 40-60: intermediate probability • >60: high probability	Not specified
Cleveland clinic prognostic score (11)	2007	- Heart rate recovery - Frequent ventricular ectopy during recovery - Other clinical/test variables	Provides 3-, 5-, and 10-year survival estimates using an online tool	Varies by result
FIT treadmill score (12)	2015	- APPMHR - Maximum achieved workload (METs) - Age - Gender	Provides 10-year survival estimates based on a continuous total score	• >100: 98% survival • 0 to 100: 97% survival • -1 to -100: 89% survival • ≤-100: 62% survival
Rancho Bernardo (13)	2015	- ST-segment deviation (mm) - Not achieving target HR - Abnormal HR recovery - Chronotropic incompetency	Each abnormal response exponentially increases CHD and all-cause mortality risk	Not specified

APPMHR: Achieved percent of predicted maximum heart rate, CHD: Coronary heart disease, HR: Heart rate

about hypercholesterolemia. Each answer is assigned a point. Then all points are added together to get a total score. According to a total score, <40 points = low probability, 40-60 points = intermediate probability, and >60 points = high probability.

Cleveland Clinic Prognostic Score (11)

This scoring scheme includes variables not present in DTS or Morise score (MS), such as heart rate recovery and the presence of frequent ventricular ectopy during the recovery period. Available as an online tool (https://riskcalc.org/SuspectedCoronaryArteryDiseaseLongTermSurvivalwNormalECG), Cleveland clinic prognostic score (CCPS) provides estimates of 3-, 5- and 10-year survival based on clinical and test variables.

FIT Treadmill Score (12)

This score was derived from the 58,020 patients in the FIT project and provides estimates of all-cause mortality based on four simple variables: achieved percent of predicted max. heart rate (APPMHR), max. achieved workload as METs, patient age, and gender.

The equation is as follows: total score = APPMHR (%) +12x (METs) - 4x (Age) +43x (if female).

Scores greater than 100, 0 to 100, -1 to -100, and less than -100 gave 10-year median survival estimates of 98%, 97%, 89%, and 62%, respectively.

Rancho Bernardo Score (13)

According to the Rancho Bernardo score (RBS), each abnormal response to specific criteria increases the incidence of coronary heart disease and all-cause mortality exponentially. There is one electrocardiographic criterion: significant ST-change, defined as ST depression or elevation of 1 mm or more. Additionally, there are three non-electrocardiographic variables: not achieving the target heart rate, defined as at least 90% of the maximal heart rate predicted for age; abnormal heart rate recovery, defined as a drop of <22 bpm after 2 minutes of recovery; and chronotropic incompetence, defined as failure to reach 80% of heart rate reserve.

Statistical Analysis

Variables are presented as mean ± standard deviation or median with interquartile range (IQR) for continuous variables and frequency (percent) for categorical variables. The normality of the variables was determined by the Kolmogorov-Smirnov test with a Lilliefors significance correction and the Shapiro-Wilk test. As the data had a nonparametric distribution, Spearman's rank correlation was used to assess how different risk scores correlate across patients. Each numeric risk score was stratified into low, intermediate, and high categories following their original publications. The agreement between categories was quantified with quadratic-weighted Cohen's κ, and a $\kappa \geq 0.61$ was considered substantial. Values were interpreted with the Landis and Koch scale.

The study was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital (approval number: 2024/186, date: 06.11.2024), and informed consent was obtained from all patients. Data analysis was conducted using the IBM SPSS Statistics software (version 26; IBM Corporation, Armonk, New York, United States).

Results

A total of 136 individuals were evaluated, with a mean age of 46±13 years; 43.4% were women. On average, participants had a body mass index (BMI) of 26.8 (±5.1), indicating an overweight profile. Notably, 24.3% had hyperlipidemia, 11.8% had diabetes, 47.8% had a family history of CAD, 25% had hypertension, and 43.4% were current or recent smokers (quit within the last year).

Regarding exercise test parameters, the mean resting heart rate was 86±15.3 bpm, while the median peak heart rate was 159 bpm (IQR) 23, reflecting a significant chronotropic response. Participants' median functional capacity was 10 METs (IQR 2.6), indicating moderate-to-good

Table 2. Characteristics of the trials that developed the risk scores

Score	Authors	Year	Size (patients)	Characteristics	Validation	Follow-up	Age (years) Gender	Notes
Duke Treadmill score	Mark et al. (15)	1987	2.842	Prospective All consecutive patients with anginal symptoms	External	Up to 10 yrs	49 (Mdn) 70% male	Most widely used yet lacks integration of patient features
Morise score	Morise et al. (10)	2003	4.640	Prospective All consecutive patients with anginal symptoms	External	2.8±1.6 yrs	50±12 53% male	One pretest score and two gender-specific exercise scores
Cleveland clinic prognostic score	Lauer et al. (11)	2007	33.268	Prospective Patients 30 years of age or older with anginal symptoms and a normal ECG	External	6.2 years (Mdn)	52 (Mdn) 62% male	Integrated analysis of ECG-related and non-ECG-related measures
FIT Treadmill score	Ahmed et al. (12)	2015	58.020	Retrospective All patients referred for an exercise stress test for any indication	Internal	10 years (Mdn)	18-96 (Mdn: 53) 51% male	Largest sample size
Rancho Bernardo	Shin et al. (13)	2015	1.789	Retrospective Asymptomatic adults	N/A	Up to 36 yrs	>20 (Mdn: 53) 47% male	Non-ECG variables had strong prognostic value

ECG: Electrocardiogram, Mdn: Median, N/A: Not applicable

exercise tolerance. The mean heart rate reserve-defined as the difference between resting and peak heart rate-was 62.9±14.9 bpm, suggesting a generally preserved cardiovascular response among this middle-aged cohort. For a full look at the features of the cohort, refer to Table 3.

Most patients scored 0 on the DTS, indicating low-risk. Only a small proportion had a score of 1 or 3. A similar pattern was observed with CCPS, as almost all patients had a score of 0, and only a small number had a score of 3; indicating that most were at low-risk. There were a significant number of patients with a FIT Treadmill score (FITTS) of 1 or 2, indicating a distribution of moderate to high-risk levels. Patients had predominantly low scores in MS, with very few showing high-risk. Finally, compared to the other scores, there was a wider distribution in RB, with more patients showing some risk. In brief, patients cluster in the low-risk band on DTS and CCPS, FITTS and MS highlight more intermediate-risk patients, and RB is the most widely scattered (see Figure 1 for a breakdown of all scores).

MS and FITTS showed the strongest association (p=0.51), suggesting these two scores share the most similarity in classifying patient risk. RBS was weakly correlated with both FITTS (p=0.05) and CCPS (p=0.09). Finally, among the other four scores, DTS shows its strongest correlation with the RBS (p=0.34), suggesting a moderate relationship between these two risk stratification methods (refer to Figure 2 for a correlation matrix heatmap).

In the quadratic-weighted Cohen's κ agreement analysis, the strongest categorical concordance was between DTS and MS (κ=0.42), followed by CCPS-MS (κ=0.37) and FITTS-CCPS (κ = 0.32). By contrast, the pair with the highest Spearman correlation coefficient in the earlier correlation analysis-MS-FITTS (p=0.51)-showed only fair agreement (κ=0.23), underscoring that rank-order similarity does not guarantee consistent three-tier risk classification. DTS-RBS achieved fair agreement (κ=0.25) despite a moderate correlation (p=0.34), whereas RBS remained only slightly interchangeable with FITTS (p=0.05; κ=0.07-0.12) and with CCPS (p=0.09; κ=0.07-0.12). all remaining score pairs exhibited slight agreement (κ=0.07-0.12), highlighting the limited substitutability of these risk-stratification metrics (Table 4).

Table 3. Baseline characteristics

	Total
Variable	(n=136)
Demographics	
Age (years)	46±13
Women	59 (43.4%)
Clinical parameters	
Body mass index (kg/m²)	26.8 (5.1)
Hyperlipidemia	33 (24.3%)
Diabetes	16 (11.8%)
Family history of CAD	65 (47.8%)
Hypertension	34 (25%)
Smoking	59 (43.4%)
Exercise test parameters	
Resting heart rate (bpm)	86±15.3
Peak heart rate (bpm) [Mdn, (IQR)]	159 (23)
Functional capacity (METs) [Mdn, (IQR)]	10 (2.6)
Heart rate reserve	62.9±14.9

bpm: Beats per minute, CAD: Coronary heart disease, Mdn: Median, IQR: Interquartile range. Smoking was defined as being an active smoker, or having quit within the last year

Table 4. Agreement between risk scores

Pair (3-tier categories)	Quadratic-weighted ϰ	Landis-koch strength
DTS vs. MS	0.42	Moderate
CCPS vs. MS	0.37	Moderate
MS vs. FITTS	0.23	Fair
DTS vs. RBS	0.25	Fair
FITTS vs. CCPS	0.32	Fair
All others	0.07-0.12	Slight

CCPS: Cleveland clinic prognostic score, DTS: Duke Treadmill score, FITTS: FIT Treadmill score, MS: Morise score, RBS: Rancho Bernardo score

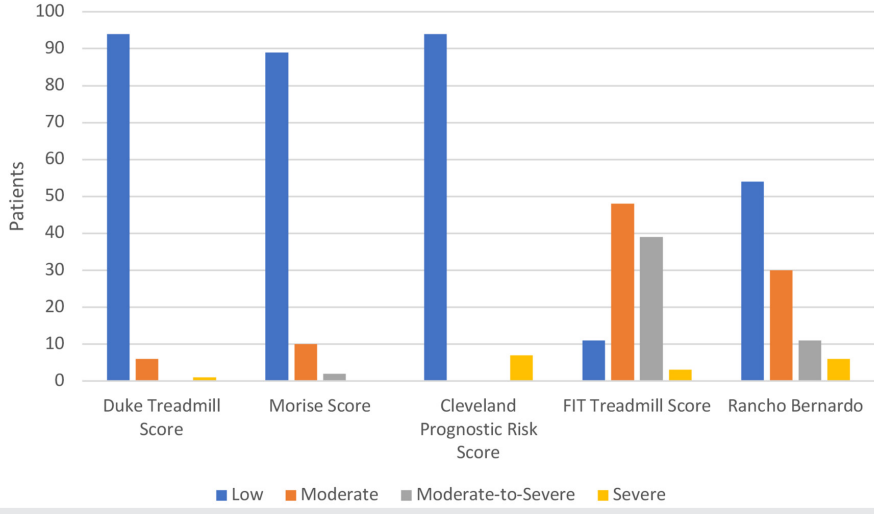

Figure 1. Distribution of the patients across five scores

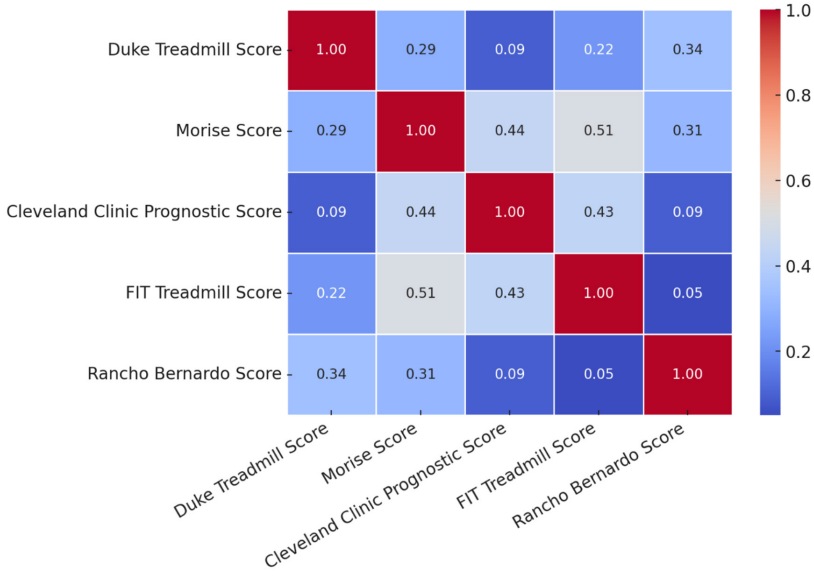

Figure 2. Spearman correlation matrix heatmap of the risk scores

Discussion

Despite strong rank correlations, agreement analysis showed only moderate concordance between certain scores and marginal agreement between others, underscoring that the scores are not interchangeable in individual patients. The loss of significance of association between MS and FITTS after further statistical analysis illustrates the fact that correlation measures parallel trends, whereas κ quantifies exact category matching. Thus, MS and FITTS, though paralleling each other (p=0.51), agree on the exact category only ~23 % better than chance.

Our finding that the MS and DTS exhibit the strongest categorical agreement is consistent with the large angiography-validated cohort analyzed by Fearon et al. (2), (n=1.282), in which both algorithms demonstrated comparable performance in detecting ≥50% stenosis (0.77±0.01 vs. 0.73±0.01, respectively). The DTS was developed to pinpoint high-risk individuals (those with a high pretest likelihood of coronary heart disease) by forecasting significant stenosis on invasive coronary angiography (≥75%), thus aiding in determining when invasive angiography is warranted for patients with chest pain. However, in people who are lower-risk and have normal test findings-especially those without symptoms-the DTS provides limited additional benefit compared to simply assessing exercise capacity. Our cohort matched the low-risk profile described in the original Duke papers, with most individuals scoring ≥5 and only a few scoring 1 or 3. By contrast, the FITTS was created for lower-risk patients whose likelihood of coronary heart disease after testing remains low; this clarifies why the DTS and FITTS do not align closely.

The FITTS and the RBS tend to assign higher-risk values overall, each with a median value of 1, while the other three scores have median values of 0. This suggests, these two scores may be more sensitive to detecting potential risk factors. However, the RBS shows weaker correlations with most other scores, indicating it may assess distinct dimensions of risk. Although the EST positivity rate in the RB study was low (approximately 6%; n=8) - a rate consistent with other studies-non-ECG measures provided robust insights into the future risk of cardiovascular mortality.

Although the FITTS and MS scores demonstrated a moderate correlation (p=0.51) and fair agreement (κ=0.23), their concordance in categorizing patients was not proportionally high. This further underscores that correlation or agreement alone does not ensure consistent risk stratification, highlighting the necessity of evaluating categorical concordance when comparing risk scores.

A moderate correlation was observed between the CCPS and the MS (κ=0.37), suggesting a fair agreement in the risk categorization of patients. Both scores include extensive clinical variables, including heart rate improvement, exercise-induced angina, and other demographic and cardiovascular factors that likely contribute to their correlation. In the derivation cohort of the original CCPS study, 64% of patients identified as moderate or high-risk by DTS were reclassified as low-risk by CCPS. Nearly all patients in our cohort scored 0; this replicated the low-risk distribution also seen in its validation cohorts. This may explain the very low correlation between CCPS and DTS in our study. In summary, both CCPS and FITTS seem to have a good discriminative capacity for low- and intermediate-risk patients, while DTS would be an ideal choice for high-risk patients who are more likely to need more advanced invasive investigations such as coronary angiography.

Almost half (43.4%) of patients smoke, a quarter (25%) have hypertension, and BMI data show a trend toward overweight and obesity (Mdn 26.8). This high prevalence of modifiable risk factors means that the population would benefit from aggressive risk factor modification and preventive interventions.

These findings under score the complementary nature of the risk scores. CCPS and MS are well suited to comprehensive assessment in data-rich clinical settings, whereas FITTS, which relies mainly on demographic factors and exercise capacity, is ideal for broad population screening. RBS adds targeted insight in special circumstances by emphasizing

non-ECG markers such as chronotropic incompetence and heart-rate recovery. Consequently, combining scores a priori may yield additive prognostic value, as each captures distinct pathophysiologic domains (e.g., chronotropic response versus METs). Clinicians should therefore select scores judiciously: CCPS can sharpen stratification in older adults or those with autonomic dysfunction, while FITTS is preferable for gauging fitness-related risk in younger, otherwise healthy individuals.

Study Limitations

This study is limited by the lack of long-term clinical outcomes (e.g., mortality or cardiac adverse events) to confirm the predictive power of these scores. Additionally, we did not include a gold standard imaging comparator, such as invasive coronary angiography or coronary CT angiography, which limits our ability to comment on the absolute diagnostic accuracy of each score in our cohort. The observed discrepancies in correlation highlight the need for studies examining whether combining multiple risk scores-potentially augmented with artificial intelligence-can improve predictive accuracy. Emerging evidence likewise indicates that machine-learning-enhanced treadmill analytics may more precisely refine risk stratification (14). Further research is needed to investigate how these variables might complement existing scores or serve as the basis of new risk models.

Conclusion

This study highlights the variability and complementary nature of treadmill-based risk scores for CAD. While DTS is effective for identifying high-risk patients needing invasive evaluation, CCPS and FITTS are better suited for lower-risk populations, and RBS adds value with non-ECG parameters. Moderate correlations and notable discrepancies among scores suggest that tailored selection enhances risk stratification. While the five treadmill-derived scores move broadly in the same direction, their modest κ values show they should not be used interchangeably for individual patient decisions. Future prospective studies should evaluate whether integrating complementary variables from more than one treadmill score can further refine clinical decision-making.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital (approval number: 2024/186, date: 06.11.2024).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 265-71
DOI: 10.4274/imj.galenos.2025.69360

Relationship of Pentraxin-3 and Suppression of Tumourigenicity 2 with Myocardial Injury in Non-Cardiac Surgery

Fatih Paşa Tatar[1], Naile Eriş Güdül[2], Mustafa Umut Somuncu[3], Bengü Gülhan Köksal[4], Uğur Köktürk[2], İlke Erbay[2], Murat Can[5]

[1]Zile State Hospital, Clinic of Cardiology, Tokat, Türkiye
[2]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Cardiology, Zonguldak, Türkiye
[3]Aydın Adnan Menderes University Faculty of Medicine, Department of Cardiology, Aydın, Türkiye
[4]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Anesthesiology and Reanimation, Zonguldak, Türkiye
[5]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Biochemistry, Zonguldak, Türkiye

ABSTRACT

Introduction: Myocardial injury after non-cardiac surgery (MINS) is a prevalent complication. It is caused by both cardiac and non-cardiac pathophysiological mechanisms. Previous studies have identified pentraxin-3 (PTX-3) and suppression of tumourigenicity 2 (ST2) as potential biomarkers associated with myocardial injury. This study is designed to evaluate the role of PTX-3 and ST2 in predicting early MINS.

Methods: This prospective observational cohort study involved patients who were deemed to be at moderate to high-risk of undergoing non-cardiac surgery. In patients with normal preoperative hs-cTnT levels, MINS was defined as a pattern of increase and/or decrease, in high-sensitivity cardiac troponin T (hs-cTnT) levels at 24 and 72 hours postoperatively. Patients without a significant change in hs-cTnT levels pre- and postoperatively were considered MINS-negative. Preoperative PTX-3 and ST2 biomarker levels were compared between MINS-positive and MINS-negative groups.

Results: The study population comprised 340 patients, of whom 79 (23.24%) were classified as MINS-positive and 261 (76.76%) as MINS-negative. PTX-3 levels were significantly higher in the MINS-positive group than in the MINS-negative group (0.24±0.11 vs. 0.021±0.06, p=0.007). There was no significant difference in the level of ST2 between the two groups of patients.

Conclusion: Elevated PTX-3 levels in the MINS-positive group suggest that this biomarker may serve as a valuable predictor of myocardial injury.

Keywords: Myocardial injury, non-cardiac surgery, biomarkers

Introduction

Despite advancements in surgical techniques and close postoperative patient monitoring, the morbidity and mortality rates in patients undergoing non-cardiac surgery remain high worldwide. Cardiovascular complications are the most prevalent cause of morbidity and mortality, with myocardial infarction (MI) being the leading cause of mortality within the initial 30 days post-surgery (1). This has led to the introduction of the term "myocardial ınjury after non-cardiac surgery" (MINS). MINS is a condition characterized by myocardial injury caused by both cardiac and non-cardiac pathophysiological mechanisms (2). MINS is often subclinical (3), which underscores the importance of early diagnosis and investigation of the underlying causes of MINS to aid in its prevention. Developing predictive markers for MINS in non-cardiac surgery could play a critical role in improving its management and outcomes.

Pentraxin-3 (PTX-3) is a multimeric acute-phase inflammatory glycoprotein that is synthesized in response to primary inflammatory signals; it has been implicated in the pathophysiology of atherosclerosis and other cardiovascular events (4). PTX-3 is expressed in endothelial cells under pro-inflammatory and pro-coagulant conditions (5). Similarly, suppression of tumorigenicity 2 (ST2), an interleukin-1 receptor family member, has emerged as a biomarker. There are two isoforms of ST2: a transmembrane receptor (ST2L) and a soluble receptor (sST2). The release of sST2 is triggered by heart failure, cardiac injury and stressful environments, making it relevant in cardiovascular assessment (6,7).

Address for Correspondence: Naile Eriş Güdül Assoc. Prof., MD, Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Cardiology, Zonguldak, Türkiye
E-mail: nailegudul@hotmail.com **ORCID ID:** orcid.org/0000-0003-4102-081X

Cite this article as: Tatar FP, Eriş Güdül N, Somuncu MU, Köksal BG, Köktürk U, Erbay İ, et al. Relationship of pentraxin-3 and suppression of tumourigenicity 2 with myocardial injury in non-cardiac surgery. İstanbul Med J. 2025; 26(4): 265-71

Received: 11.03.2025
Accepted: 21.07.2025
Publication Date: 12.11.2025

This study aims to evaluate whether biomarkers PTX-3 and sST2 are associated with MINS in medium- and high-risk non-cardiac surgery patients.

Methods

Study Population

The calculation was made of the minimum number of patients required for an effect size of 0.2, in conjunction with a 90% power analysis. In this observational and prospective study, 340 patients who underwent non-cardiac surgery at medium and/or high-risk, and did not have postoperative symptoms of myocardial ischemia, were included. Ethical approval was obtained from the Ethics Committee for Non-Invasive Clinical Research, Faculty of Medicine, Zonguldak Bülent Ecevit University (approval number: 2021/14, date: 28.07.2021). Between October 1, 2021, and October 1, 2022, a total of 340 patients aged over 40 years who underwent medium- and/or high-risk non-cardiac surgery at Zonguldak Bülent Ecevit University Health Practice and Research Center were enrolled after providing informed consent. The classification of surgeries as medium- or high-risk was based on the European Society of Cardiology guidelines on "cardiovascular assessment and management in non-cardiac surgery" (8). The study flowchart, detailing the inclusion and exclusion criteria, is presented in Figure 1.

High-sensitivity cardiac troponin T (hs-cTnT) levels were measured preoperatively and at 24 and 72 hours postoperatively. A 12-lead electrocardiogram (ECG) was performed in patients with a post-operative pattern of increase or decrease in hs-cTnT levels. Echocardiography was performed to rule out wall motion abnormalities if the post-operative ECG showed changes from the preoperative ECG. Patients were classified as "MINS positive" if they had evidence of myocardial injury, but no ECG findings or symptoms of ischaemia. Conversely, patients with normal hs-cTnT levels at all time points (preoperatively and at 24 and 72 hours postoperatively) were classified as MINS-negative.

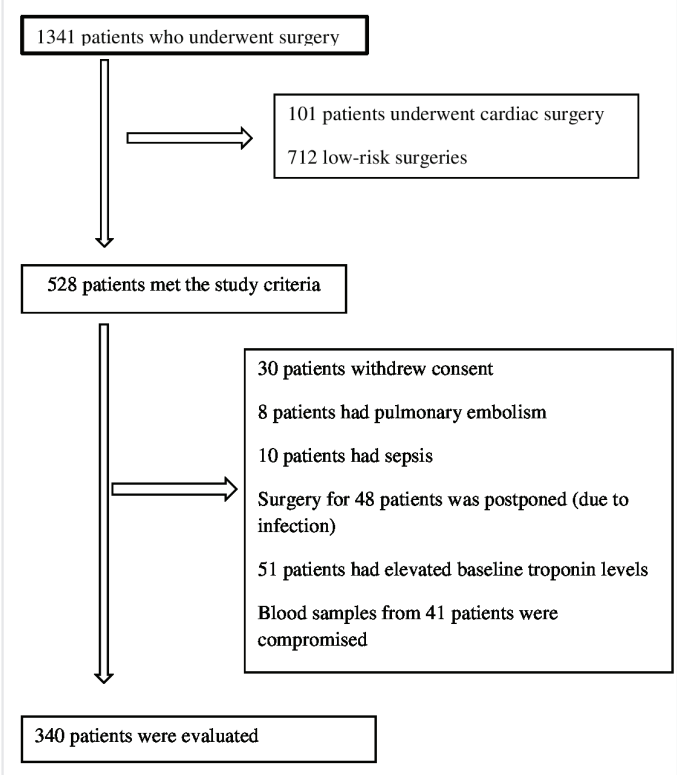

Figure 1. Inclusion criteria for the study population

Sample Collection and Biomarker Analysis

Preoperative demographics, risk factors, comorbidities, medical history, medications, laboratory parameters, and perioperative data were recorded for all patients. Peripheral venous blood samples (5 mL) were collected on admission to hospital and placed in EDTA-coated vacuum tubes. The samples were immediately centrifuged at 3000 rpm for 15 minutes. The serum was separated and stored at -70 °C until analysis.

Serum levels of PTX-3 (SEK411Hu, Cloud-Clone Corp., Katy, Texas, USA) and sST2 (SED171Hu, Cloud-Clone Corp., Katy, Texas, USA) were measured using ELISA kits according to the manufacturer's protocol. The minimum detectable concentration for PTX-3 was 6000-9375 pg/mL, with intra- and inter-assay coefficients of variation of <10% and <12%, respectively. For sST2, the minimum detectable concentration was 0.156-10 ng/mL, with intra- and inter-assay coefficients of variation of <10% and <12%, respectively.

Myocardial injury was defined as an increase in hs-cTnT above the 99th percentile upper reference limit (URL) within 24 hours of surgery. Non-ischemic causes of elevated hs-cTnT such as atrial fibrillation (AF), pulmonary embolism, sepsis, or chronically high baseline values were excluded.

Definition of MINS

MINS is primarily ischemic in nature. However, the classic symptoms associated with MI, such as chest pain or shortness of breath, can often be obscured during the perioperative period due to the effects of sedation and analgesia. As a result, typical signs of myocardial ischemia might not manifest clearly on an ECG. MINS is defined as an elevation in the levels of hs-cTnI above the 99th percentile URL, accompanied by a dynamic pattern of rise and/or fall. While most cases occur within the first 72 hours after non-cardiac surgery, MINS can develop up to 30 days postoperatively. It is essential to distinguish MINS from other non-ischemic causes of myocardial injury, such as pulmonary thromboembolism, sepsis, AF, acute decompensated congestive heart failure, renal failure, and cardioversion. These causes are excluded from its definition.

Statistical Analysis

All statistical analyses were performed using SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Normality of data distribution was assessed using both visual and analytical methods. Descriptive statistics are presented as means ± standard deviations for normally distributed variables and as medians with interquartile ranges for variables that are not normally distributed. Categorical variables are expressed numerically as either whole numbers or percentages. A series of comparisons between groups was conducted, with the unpaired Student's t-test utilized for normally distributed continuous variables, the

Mann-Whitney U test employed for non-normally distributed variables, and the chi-squared test applied to categorical variables. Independent predictors of myocardial injury were determined using univariate and multivariate logistic regression analyses, and 95% confidence intervals (CI) and odds ratios (OR) were shown. As the cut-off values for PTX-3 and C-reactive protein (CRP) vary in the literature due to different methods and kits, the values obtained from the receiver operating characteristics (ROC) analysis were used to stratify the study population into four groups using a 2 x 2 approach. The ability of these groups to predict myocardial injury was analyzed using the low CRP/low PTX-3 group as the reference category. p-values of <0.05 were considered statistically significant.

Results

Baseline Characteristics

All study participants were classified, of whom 79 (23.24%) were as MINS (+) and 261 (76.76%) as MINS (-). There were no statistically significant differences between the two groups in terms of sex, age, BMI, comorbidities (e.g,. hypertension, diabetes mellitus) or medication use (p>0.05 for all, Table 1).

Laboratory Findings

Postoperative laboratory analysis revealed significantly higher PTX-3 levels in the MINS (+) group compared to the MINS (-) group (0.24±0.11 vs. 0.021±0.06, p=0.007). Similarly, CRP levels were elevated in the MINS (+) group (23.5±39.1 vs. 15.8±26.5, p=0.047). However, no significant differences were observed for other biomarkers, such as sST2 (p=0.202, Table 2).

Perioperative Characteristics

Perioperative data demonstrated a higher prevalence of emergency surgery in the MINS (+) group (19% vs. 9.2%, p=0.017), a higher prevalence of use of general anesthesia (91.1% vs. 79.7%, p=0.019), and higher ASA scores (12.7% vs. 8.0%, p=0.038). A revised cardiac risk index (RCRI) >3 was also significantly more common in the MINS (+) group (15.2% vs. 5.7%, p<0.001).

Perioperative complications including hypotension (46.8% vs. 33.3%, p=0.029), bradycardia (25.3% vs. 13%, p=0.009), hypoxia (10.1% vs. 2.7%, p=0.005) and vasopressor requirement (5.1% vs. 1.1%, p=0.032) were significantly more common in the MINS (+) group. In addition, the duration of surgery was longer in the MINS (+) group than in the MINS (-) group (186±95 vs. 159±77 minutes, p=0.020, Table 3).

Predictors of Myocardial Injury

Logistic regression analysis identified CRP (p=0.012), use of general anesthesia (p=0.030), bradycardia (p=0.005), intraoperative hypoxia (p=0.016), and a RCRI score greater than 3 (p=0.025) as independent predictors of myocardial injury. Additionally, PTX-3 levels were found to be an independent predictor of MINS (OR: 1.043; 95% CI: 1.011-1.075; p=0.008) (Table 4).

ROC Analysis for PTX-3 and CRP

ROC curve analysis revealed a cut-off value of 0.21 pg/mL for PTX-3 in predicting myocardial injury, with an area under the curve of 0.734 (95% CI: 0.612-0.856, p=0.004). This cut-off showed a sensitivity of 69.2% and a specificity of 61.7% (Figure 2).

Table 1. Baseline clinical characteristics of patients

	Post-op MINS (-) (n=261; 76.76%)	Post-op MINS (+) (n=79; 23.24%)	p-value
Age (years)	65.95±11.2	67.58±11.48	0.295
Male n (%)	123 (47.1)	40 (50.6)	0.585
BMI (kg/m²)	29.56±6.44	29.49±6.24	0.938
Baseline SKB (mmHg)	127.6±63.3	125.9±17.1	0.440
Baseline DKB (mmHg)	74.3±11.1	72.9±10.2	0.218
Baseline HR (beats/min)	79.7±11.8	80.1±12.8	0.794
Smoking, n (%)	48 (18.4)	15 (19.0)	0.905
HT, n (%)	178 (68.2)	49 (62.0)	0.307
DM, n (%)	95 (36.4)	31 (39.2)	0.647
HL, n (%)	54 (20.7)	18 (22.8)	0.690
COPD, n (%) Medical treatment	49 (18.8)	16 (20.3)	0.770
OAC, n (%)	24 (9.2)	6 (7.6)	0.660
Antiplatelet agent, n (%)	68 (26.1)	26 (32.9)	0.232
Beta blocker, n (%)	67 (25.7)	17 (21.5)	0.454
ACEi/ARB, n (%)	53 (20.3)	16 (20.3)	0.992

MINS: Myocardial injury after non-cardiac surgery, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, COPD: Chronic obstructive pulmonary disease, ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blockers

Table 2. Laboratory variables of patients

	Post-op MINS (-) (n=261;76.76%)	Post-op MINS (+) (n=79; 23.24%)	p-value
Creatinine (mg/dL)	0.88±0.36	0.85±0.28	0.517
LDL (mg/dL)	101.2±34.7	105.6±36.7	0.328
HDL (mg/dL)	43.1±12.5	43.5±13.7	0.940
Triglycerides (mg/dL)	150.6±80.2	153.0±106.3	0.742
Total cholesterol (mg/dL)	174.6±42.2	179.9±42.2	0.433
Glucose (mg/dL)	119.7±40.5	127.7±38.9	0.135
WBC (10³/µL)	8.37±2.55	8.92±2.47	0.091
Hgb (g/dL)	11.86±1.88	11.97±1.74	0.633
Plt (10³/µL)	263.1±102.9	245.7±84.3	0.173
N/L ratio	5.23±4.47	6.45±8.2	0.090
MPV (fL)	8.86±1.04	8.78±0.97	0.218
ALT	19.2±16.7	23.7±61.1	0.290
PTX-3 (pg/mL)	0.021±0.06	0.24±0.11	0.007
CRP (mg/dL)	15.8±26.5	23.5±39.1	0.047
sST2 (ng/mL)	3.45±1.67	3.72±1.62	0.202

MINS: Myocardial injury after non-cardiac surgery, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, Hgb: Hemoglobin, N/L: Neutrophil/lymphocyte ratio, MPV: Mean platelet volume, ALT: Alanine aminotransferase, PTX-3: Pentraxin-3, CRP: C-reactive protein, sST2: Soluble ST2

Patients were further stratified according to PTX-3 and CRP levels. Compared to the reference group (low CRP/low PTX-3), the low CRP/high PTX-3 group was associated with an increased risk of myocardial injury (OR: 2.68, 95% CI: 1.30-5.49, p=0.007), while the combination of high CRP and high PTX-3 levels showed the strongest predictive ability (OR: 4.22, 95% CI: 1.99-8.96, p<0.001). The high CRP/low PTX-3 group did not reach statistical significance (OR: 2.28, 95% CI: 0.98-4.93, p=0.054) (Figure 3).

Table 3. Perioperative characteristics of patients

	Post-op MINS (-) (n=261; 76.76%)	**Post-op MINS (+) (n=79; 23.24%)**	**p-value**
Emergency surgery, n (%)	24 (9.2)	15 (19.0)	0.017
Type of anesthesia			0.019
General, n (%)	208 (79.7)	72 (91.1)	
Epidural, n (%)	53 (20.3)	7 (8.9)	
ASA Score, n (%)			0.038
1	14 (5.4)	3 (3.8)	
2	91 (34.9)	15 (19.0)	
3	135 (51.7)	51 (64.6)	
4	21 (8.0)	10 (12.7)	
Func. Mets, n (%)			0.087
<1	29 (11.1)	14 (17.7)	
1-4	75 (28.7)	28 (35.4)	
4-10	157 (60.2)	37 (46.8)	
Revised cardiac risk index, n (%)			<0.001
0-1	205 (78.6)	46 (58.2)	
2	41 (15.7)	21 (26.6)	
>3	15 (5.7)	12 (15.2)	
CAD, n (%)	53 (20.3)	31 (39.2)	0.001
CHF, n (%)	37 (14.2)	19 (24.1)	0.038
CVD, n (%)	31 (11.9)	14 (17.7)	0.179
Receiving insulin therapy, n (%)	66 (25.3)	24 (30.4)	0.369
Creatinine >2 mg/dL, n (%)	23 (8.8)	11 (13.9)	0.185
Type of surgery, n (%)			0.135
Thoracic	5 (1.9)	1 (1.3)	
Orthopedic/neurosurgery	166 (63.6)	45 (57.0)	
Gastrointestinal	25 (9.6)	5 (6.3)	
ENT	12 (4.6)	2 (2.5)	
Gynecology/urology	18 (6.9)	13 (16.5)	
Hepatobiliary	35 (13.4)	13 (16.5)	
Perioperative complications, n (%)			
Hypotension	87 (33.3)	37 (46.8)	0.029
Hypertension	129 (49.4)	40 (50.6)	0.851
Bradycardia	34 (13.0)	20 (25.3)	0.009
Tachycardia	23 (8.8)	13 (16.5)	0.053
Hypoxia	7 (2.7)	8 (10.1)	0.005
Blood loss (mL)	137±231	245±473	0.052
Total transfusion (mL)	2166±1003	2489±1382	0.057
Surgery duration (minutes)	159±77	186±95	0.02
Intraoperative vasopressor use, n (%)	3 (1.1)	4 (5.1)	0.032

MINS: Myocardial injury after non-cardiac surgery, ASA: American Society of Anesthesiologists, Func. Mets: Functional metabolic equivalent (functional capacity), CAD: Coronary artery disease, CHF: Congestive heart failure, CVD: Cerebrovascular disease, ENT: Ear, nose, and throat

Table 4. Predictors of perioperative myocardial injury

Variables	Univariate analysis Odds ratio (CI 95%)	p-value	Multivariate analysis Odds ratio (CI 95%)	p-value
CRP (per 1 mg/dL)	1.006 (1.002-1.022)	**0.018**	1.011 (1.002-1.019)	**0.012**
General anesthesia	2.9 (1.105-7.153)	**0.019**	2.70 (1.10-6.63)	**0.030**
Bradycardia	2.82 (1.046-4.048)	**0.004**	2.69 (1.35-5.33)	**0.005**
Hypoxia	4.11 (1.23-9.35)	**0.009**	3.99 (1.29-12.34)	**0.016**
Revised cardiac risk index >3	2.05 (1.006-7.1159	**0.029**	2.76 (1.13-6.74)	**0.025**
Pentraxin-3 x100	1.033 (1.007-2.262)	**0.012**	1.043 (1.011-1.075)	**0.008**
DM	1.525 (1.001-3.128)	**0.047**	1.323 (0.852-3.332)	0.116
CAD	1.496 (0.244-1.728)	0.272		
Emergency surgery	1.946 (0.601-2.504)	0.118		
HT	1.467 (0.840-2.971)	0.056		

CI: Confidence interval, CRP: C-reactive protein, DM: Diabetes mellitus, CAD: Coronary artery disease, HT: Hypertension

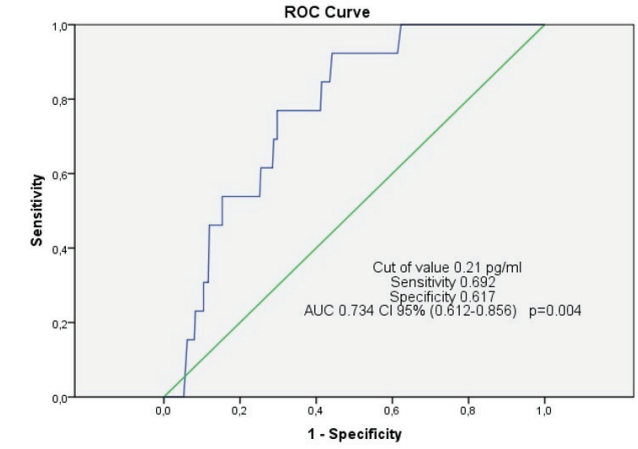

Figure 2. ROC curve demonstrating the discriminative ability of pentraxin-3 levels for myocardial injury
AUC: Area under the ROC curve, CI: Confidence interval, ROC: Receiver operating characteristics

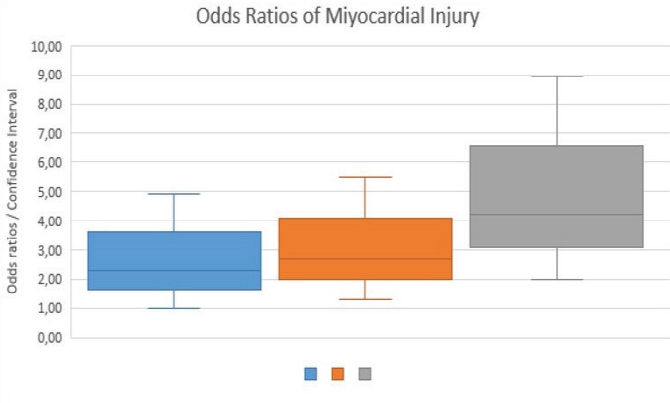

Figure 3. Predictive value of perioperative PTX-3 and CRP levels for myocardial injury
Blue bar: High CRP/Low PTX-3 group, Orange bar: Low CRP/High PTX-3 group, Gray bar: High CRP/High PTX-3 group
CRP: C-reactive protein, PTX-3: Pentraxin-3

Discussion

This observational study investigates the association between MINS and the biomarkers PTX-3 and sST2 in patients undergoing non-cardiac surgery at a medium to high-risk. The results demonstrated that there was a significant increase in PTX-3 levels in patients diagnosed with MINS, suggesting its potential role as a predictive biomarker of perioperative myocardial injury. In contrast, sST2 levels were not significantly different between groups.

MINS is a frequently overlooked postoperative complication associated with significant adverse outcomes, yet it remains largely underdiagnosed due to its asymptomatic nature and the absence of routine screening protocols. Most cases are only detected through elevated hs-cTnT levels. The VISION study provided a critical insight into the burden of MINS, reporting that 17.9% of patients aged 45 years and older who underwent non-cardiac surgery developed MINS, with 93.1% of cases asymptomatic (9). Furthermore, elevated perioperative hs-cTnT levels were strongly associated with increased 30-day mortality, highlighting the importance of systematic postoperative troponin monitoring in high-risk patients (9). These findings have been further validated by large cohort studies, which consistently highlight the prognostic significance of perioperative troponin elevation (3,10).

Despite its high prevalence and prognostic implications, MINS is often unrecognised by traditional clinical assessment and risk scores. While the incidence of acute coronary syndrome requiring revascularization after non-cardiac surgery is less than 0.2% (11), the silent nature of MINS highlights the need for more effective pre- and post-operative risk stratification (2,3,12,13). The current study contributes to this understanding by identifying PTX-3 as a potential biomarker for MINS, providing an additional tool for early detection in patients undergoing moderate- or high-risk surgery.

As an inflammatory biomarker, elevated PTX-3 levels are commonly detected in atherosclerotic lesions, underscoring its potential as a marker of vascular damage (14). Released from endothelial cells during localized vascular inflammation, PTX-3 has emerged as a promising diagnostic tool for acute cardiovascular events. Studies by Matsuura

et al. (15) and Turkmen et al. (16) have shown that PTX-3 levels are significantly higher in atherosclerotic patients and in patients with AMIs, and have linked PTX-3 to systemic inflammation and endothelial dysfunction, key mechanisms in coronary artery disease (CAD) (17). A meta-analysis has also confirmed that elevated levels of PTX-3 are independently associated with an increase in all-cause mortality and cardiac mortality in patients with CAD (18). Similarly, Peri et al. (19) reported significantly higher PTX-3 and CRP levels in AMI patients compared to healthy controls, reinforcing the utility of PTX-3 as a biomarker for cardiovascular risk stratification.

In our study, PTX-3 emerged as an important independent predictor of MINS. Furthermore, high preoperative PTX-3 and CRP levels were strongly associated with myocardial damage, reinforcing their role as valuable biomarkers for identifying high-risk patients. Patients with a history of CAD or heart failure were more likely to develop MINS, which highlights the importance of considering such pre-existing cardiovascular conditions in perioperative risk assessment.

A thorough preoperative cardiovascular risk evaluation may facilitate the identification of patients with an elevated probability of developing MINS. Perioperative risk assessments and PTX-3/CRP values can guide perioperative management and prevent MINS from being underestimated. Patients considered to be at high-risk of MINS may require modifications to their intraoperative care, including the initiation of secondary prophylactic interventions, invasive arterial pressure monitoring, strategies to prevent hypotension, and systematic preoperative and postoperative cTn monitoring. It is hypothesised that improvements in the diagnosis and understanding of MINS will ultimately result in enhanced postoperative outcomes following non-cardiac surgery.

Study Limitations

The present study is subject to several limitations. Because this was conducted as a single-centre study, the results may have limited generalizability, despite the homogeneity of the sample and the use of a standardised surgical protocol. Comparability with other studies is further challenged by variations in the ELISA kits used for biomarker measurements. In addition, PTX-3 levels were measured only once preoperatively, with no follow-up samples to assess postoperative changes that might influence outcomes. Finally, the initial sample size was not fully maintained, and thus the results should be interpreted as preliminary. Larger, multicenter studies with serial measurements of PTX-3 before and after surgery are needed to better elucidate its clinical significance and impact.

Conclusion

The present study's findings suggest that PTX-3 may serve as a valuable biomarker for predicting MINS in patients undergoing non-cardiac surgery. The strong association between elevated preoperative PTX-3 and CRP levels and myocardial injury highlights their potential role in identifying high-risk patients. These results support the need for further studies to evaluate the clinical utility of PTX-3.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee for Non-invasive Clinical Research, Faculty of Medicine, Zonguldak Bülent Ecevit University (approval number: 2021/14, date: 28.07.2021).

Informed Consent: All participants provided informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - F.P.T., B.G.K.; Concept - N.E.G., M.U.S.; Design - N.E.G., M.U.S., B.G.K., M.C.; Data Collection or Processing - F.P.T., B.G.K., M.C., U.K.; Analysis or Interpretation - U.K., İ.E.; Literature Search - F.P.T., N.E.G., M.U.S., B.G.K., U.K., İ.E., M.C.; Writing - F.P.T., N.E.G., M.U.S., İ.E.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 272-8
DOI: 10.4274/imj.galenos.2025.37786

Comparison Between the Efficacy of Standard Prophylactic Medical Treatment, Wet Cupping Therapy and Dry Cupping Therapy on Migraine Without Aura: A Randomized Clinical Trial

Esra Karabal Arda[1], Arzu İrban[2], Tuğba Okluoğlu[3]

[1]University of Health Sciences Türkiye, Department of Traditional and Complementary Medicine, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Department of Anesthesiology and Reanimation, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Neurology, İstanbul, Türkiye

ABSTRACT

Introduction: Cupping therapy has been used in many societies for the treatment of various diseases, with its history dating back thousands of years. The use of cupping therapy is mentioned in an Egyptian papyrus from 1550 B.C. and also in the inscriptions of Herodotus in the 400s B.C. It was proven that it was used early in Chinese medicine. It is well known that there are many sources on the use of cupping therapy in Anatolia.

Methods: Migraine is a common headache disorder today. This study was conducted as a multicenter study with the approval of the Traditional and Complementary Medicine Clinical Research Ethics Committee to investigate the effects of wet and dry cupping therapy in treating migraine without aura. In the prospective randomized controlled study conducted with the closed envelope technique, patients were divided into three groups: the first group received 6 sessions of wet cupping, the second group received 6 sessions of dry cupping, and the third group received prophylactic conventional drug therapy. The results of the groups were compared at the end of the treatment.

Results: It is observed that wet cupping therapy significantly and statistically reduced anxiety and depression levels in the treatment of migraine without aura, and significantly increased the quality of life of the patients. It is observed that dry cupping therapy significantly increased the quality of life of patients.

Conclusion: Cupping therapy is effective in the treatment of migraine without aura. While wet cupping therapy, dry cupping therapy, and prophylactic drug therapy are preferred, the effectiveness of these methods, along with their side effects and cost, should be evaluated. The method that will best benefit the patient should be preferred.

Keywords: Traditional and complementary medicine, ıntegrative medicine, cupping therapy, migraine, anatolian medicine

Introduction

Migraine is the most common headache disorder worldwide, reducing the individual's quality of life and productivity, and causing loss of productivity at work (1). It can be triggered by normal physical activity. It may be related to hunger/satiety status and sensitivity to sound and light may be accompanied by nausea and vomiting. Migraine is divided into two types: with aura and without aura, although there are many variations. The most common version is without aura (2,3). Migraine treatment is divided into attack treatment (acute) and prophylactic treatment (chronic) (4). The main aim is to prevent attacks. Avoiding things that cause attacks is the first step of treatment.

Acute treatment (attack treatment): The goal of acute treatment aims to end the attack as soon as possible. Simple analgesics, NSAIDs, and antiemetics are the most commonly used drugs before or during an attack (5).

Chronic treatment (prophylactic treatment): It is preferred in patients who experience more than 2 severe attacks per month; their attacks continue periodically, lasting between 4 and 72 hours. Reducing the frequency of attacks is the main goal. Beta-blockers, calcium channel blockers, antiepileptics, and antidepressants are the most commonly used drugs (5).

Address for Correspondence: Esra Karabal Arda MD, University of Health Sciences Türkiye, Department of Traditional and Complementary Medicine, İstanbul, Türkiye
E-mail: esrakarabalarda@gmail.com **ORCID ID:** orcid.org/0009-0004-9494-1553

Cite this article as: Karabal Arda E, İrban A, Okluoğlu T. Comparison between the efficacy of standard prophylactic medical treatment, wet cupping therapy and dry cupping therapy on migraine without aura: a randomized clinical trial. İstanbul Med J. 2025; 26(4): 272-8

Received: 12.08.2024
Accepted: 23.09.2025
Publication Date: 12.11.2025

Cupping therapy is one of the most valuable treatment methods applied in Anatolian lands (6). Its use is indicated in many diseases. It can be used not only as a therapeutic method and complementary method but also prophylactically to prevent many diseases.

With cupping therapy, local blood flow is accelerated, capillary circulation is improved, capillary endothelial cells are repaired, granulation is accelerated, and angiogenesis begins in the regional tissue. The functioning of the lymphatic system is regulated. The neuro-endocrine-immune modulation mechanism states that immunomodulation is achieved by stimulating the skin surface and increasing capillary permeability, by spreading signal molecules, and by triggering the release of cytokines by these signal molecules. At the same time, neuromodulation occurs through the stimulation of nerve endings (7-9).

With the activation of the hemoxygenase-1 system, antioxidant, anti-inflammatory, anti-apoptotic, and immunomodulatory effects are observed, and vasodilation and antinociception occur (10).

The adaptation problems to chronic drug treatment, including side effects and toleration issues, addiction to long-term (acute or chronic) drugs, frequent use of painkillers triggering migraine attacks, and the insufficiency of acute or chronic drugs to reduce the frequency and severity of migraine attacks, pose significant challenges. Therefore, this study aims to prove the effectiveness of wet and dry cupping therapy in the treatment of migraine without aura.

This study aims to demonstrate the effectiveness of wet and dry cupping therapy in patients aged 18-58 diagnosed with migraine without aura through a randomized controlled trial.

Methods

The study was conducted with 75 patients at the traditional and complementary medicine center of a training and research hospital, another traditional and complementary medicine center at a different training and research hospital, and the Neurology Clinic of a training and research hospital between March 2021 and December 2022. The study was approved by the GETAT Clinical Research Ethics Committee (approval number: 2024-052, date: 30.04.2024). All participants read and signed the informed consent form.

To determine the sample size, power analysis was performed using the G*Power 3.1.9.4 program. While determining the sample size of the designed research, the significance level was taken as α=0.05 (11). Changing efficacy of wet cupping therapy in migration with lunar phase: a self-controlled interventional study. Considering the reference article "Medical Science Monitor: International Medical Journal of Experimental and Clinical Research", it was concluded that at least 57 subjects in total should be included in the sampling with 80% power. In our study, 75 patients were included.

Inclusion and Exclusion Criteria

The patients we included in our study were those who had migraine attacks at least twice a month for more than 3 months, were between the ages of 18 and 58, and were diagnosed with migraine without aura. Those who had migraine attacks only during the perimenstrual period, those who had head and neck surgery, pregnant women, patients diagnosed with cancer, and patients with bleeding problems were not included in the study.

Study Design

In a randomized controlled study, patients who were diagnosed with migraine without aura and met the study criteria were randomly divided using a sealed envelope method into 3 different groups.

- Study group I (group wet cupping, IK; n=25) consists of patients who received 6 sessions of wet cupping therapy.
- Study group II, group dry cupping (KK) with n=25, consists of patients who received 6 sessions of dry cupping therapy.
- Study group III ([drug (N) n=25] consists of patients given standard prophylactic drug treatment by a neurologist.

Group I

In the first group, 25 patients were included; 1 patient was excluded because he did not attend the sessions.

Patients in the first group (group I) [wet cupping (IK), n=24] underwent 6 sessions of wet cupping therapy, with the first four sessions planned at 15-day intervals and the last two sessions planned at 1-month intervals.

Wet cupping therapy application points were determined as the occipital protrusion (OP) located approximately 1.5 cm above the external occipital protuberance, 3 points in the interscapular region, and the C7 vertebra point (Figure 1).

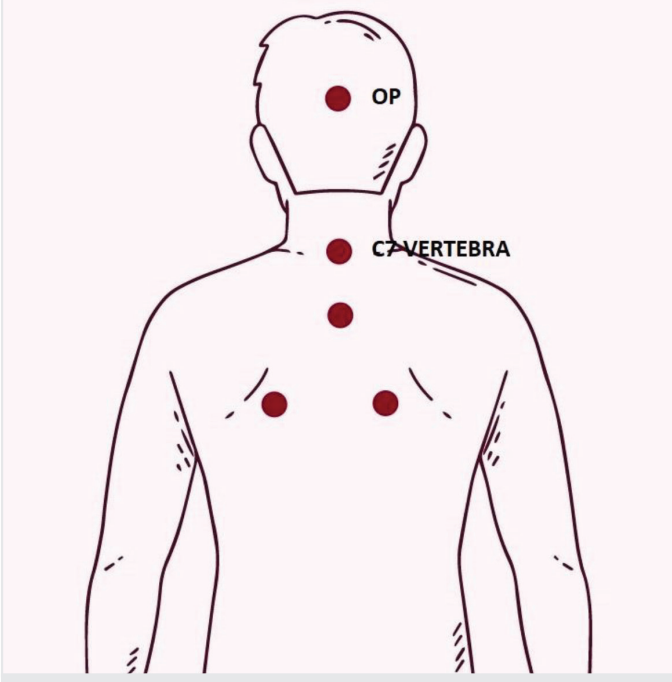

Figure 1. Cupping therapy points
OP: Occipital protrusion

Group II

Patients in the second group [group dry cupping (KK)-n=25] underwent 6 sessions of dry cupping therapy, with the first four sessions planned at 15-day intervals and the last two sessions planned at 1-month intervals.

Dry cupping therapy application points were determined as the OP located approximately 1.5 cm above the external occipital protuberance, 3 points in the interscapular region, and the C7 vertebra point.

Group III

The twenty-five patients were included in the third group (group III). Three patients were excluded from the study because they did not attend routine visits.

Patients in the third group, group pharmaceuticals I (n=22), were initiated on standard prophylactic treatment by the neurologist.

The patients in the third group of the study were scheduled to visit the doctor every month.

All volunteer patients in all three groups were informed about the study process and read, understood, and signed the informed volunteer consent form.

On the first day of the study, corresponding to the 1st session of cupping application, the volunteer patients received the prescribed prophylactic drug treatment. In the 2nd month (the 3rd session in cupping), the 3rd month (the 5th session in cupping application), and the 4th month (the 6th session of cupping), prior to the outpatient clinic examination/session, the following assessments were conducted: headache case evaluation form, visual analogue score (VAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Allodynia Symptom Scale, and World Health Organization Quality of Life Scale – 8-akademik kullanımı bu şekilde ama yazar ne derse o tbi xD (WHOQOL-8). The results of the BDI, BAI, and WHOQOL-8 were analyzed in this study.

Wet Cupping Therapy Method

In the wet cupping therapy group, a triple technique was used (vacuuming-incision-vacuuming). The application areas (Figure 1) were cleaned with Betadine. The scalp has been cleaned. At the OP point, a plastic cup suitable for vacuuming with a diameter of 3 centimeters (cm) was used, and at the interscapular region and C7 point, disposable plastic cups with a diameter of 6 cm were used.

The first vacuuming process before the incision is 30 seconds at the OP point and 2 minutes at the interscapular and C7 point. It's made to last. After the first vacuuming, the incision was made. The incisions are made with a scalpel tip, with an average depth of 1 mm and an average length of 5-7 mm. It was applied parallel to the muscles in the region. At each cup point, an average of 10-12 incisions was made in the head region and 18-20 incisions in the back region. The vacuuming process applied after the incision takes approximately 1-2 minutes at the OP point and 3-5 minutes at the interscapular and C7 points, and it has been implemented on an ongoing basis. The third vacuum procedure on the cleaned areas takes approximately 1-2 minutes at the OP point and 3-5 minutes at the interscapular and C7 points, and has been implemented on an ongoing basis (Figure 1).

Dry Cupping Method

Dry cupping was applied in a similar way to wet cupping, but without an incision.

Statistical Analysis

Descriptive statistics of the study data included mean, standard deviation, median, minimum and maximum values, frequency, and ratios. The Kolmogorov-Smirnov test was used to assess data distribution. For independent quantitative data analysis, the Kruskal-Wallis and Mann-Whitney U tests were applied, while the Wilcoxon test was used for dependent quantitative data. All analyses were conducted using SPSS 25.0.

Participants were divided into three groups:

- **Group I:** Wet cupping therapy
- **Group II:** Dry cupping therapy
- **Group III:** Conventional prophylactic drug therapy

The study sample consisted predominantly of female participants (58 women, 13 men), with an average age of 37.87.

Results

Table 1 shows how BAI scores changed over time in three different groups. The mean baseline BAI score in group I was 18.17, in group II it was 17.76, and in group III it was 9.36. There is a statistically significant difference in baseline data between groups (p=0.003). In this case, it is more meaningful to examine the change within the group rather than the difference between groups.

Beck Anxiety Inventory

It is observed that there is a statistically significant change in the anxiety level in group I at the 3rd and 4th months compared to the beginning (p=0.01 and p=0.000).

There is no statistically significant change in the anxiety level in group II during the 2nd, 3rd, and 4th months compared to the baseline (p=0.165, p=0.954, and p=0.411).

It is observed that there is a statistically significant change in the anxiety level in group III in the second and third months compared to the beginning. However, there was no statistically significant change compared to the beginning of the 4th month (p=0.051).

According to the post-hoc test based on the initial data, there is a statistically significant difference between group I and group III in the BAI. There is no significant difference between group I and group II. There is a significant difference between group II and group III.

In group I, a significant decrease was observed in the BAI score at the 4th month compared to the beginning (p<0.05). The anxiety-reducing effect of wet cupping therapy is statistically proven. It should not be ignored that the change in group III's BAI score from the beginning to the 4th month was a borderline value for it to be statistically significant (p=0.051).

Table 2 shows how BDI scores changed over time in three different groups. The mean baseline BDI score in group I was 13.21, in group

Table 1. Beck Anxiety Inventory change analysis

		Group I			Group II			Group III			p	
Beck Anxiety Inventory												
Starting date	M ± SD	S	±	10.83	17.76	±	11.70	9.36	±	9.08	**0.003**	K
	Median	15.00			17.00			8.00				
Change compared to the start												
2nd month change	M ± SD	-2.29	±	7.03	1.40	±	10.47	-1.00	±	1.72	**0.021**	K
	Median	-2.50			2.00			-0.50				
In group change p		0.103		W	0.165		W	**0.011**		W		
3rd month change	M ± SD	-3.96	±	6.23	-0.04	±	10.86	-2.09	±	2.31	**0.038**	K
	Median	-3.50			1.00			-2.00				
In group change p		**0.001**		W	0.954		W	**0.001**		W		
4th month change	M ± SD	-6.50	±	7.06	-1.52	±	10.50	-1.46	±	4.03	**0,018**	K
	Median	-5.50			-1.00			-0.50				
In group change p		**0.000**		W	0.411		W	0.051		W		

K: Kruskal-wallis (Mann-whitney u test), W: Wilcoxon test, SD: Standard deviation, M: Mean

Table 2. Beck Depression Inventory change analysis

		Group I			Group II			Group III			p	
Beck Depression Inventory												
Starting date	M ± SD	13.21	±	8.25	14.12	±	7.36	14.17	±	8.47	0.922	K
	Median	12.50			12.00			14.00				
Change compared to the start												
2nd month change	M ± SD	-3.17	±	6.29	-0.92	±	5.05	-1.00	±	1.53	0.707	K
	Median	-1.50			-1.00			-0.50				
In group change p		0.063		W	0.337		W	**0.006**		W		
3rd month change	M ± SD	-3.33	±	7.48	-2.64	±	7.00	-2.17	±	2.74	0.763	K
	Median	-2.50			-3.00			-3.00				
In group change p		**0.032**		W	**0.048**		W	**0.003**		W		
4th month change	M ± SD	-3.83	±	7.87	-3.04	±	8.37	-4.00	±	6.37	0.732	K
	Median	-3.00			-3.00			-3.00				
In group change p		**0.034**		W	0.108		W	**0.004**		W		

K: Kruskal-wallis (Mann-whitney u test), W: Wilcoxon test, SD: Standard deviation, M: Mean

II it was 14.12, and in group III it was 14.17. There is no statistically significant difference in baseline data between groups (p=0.922). In this case, comparisons can be made between the three groups.

Beck Depression Inventory

In group I, a statistically significant change in the depression level was observed in the 3rd and 4th months compared to baseline (p=0.032 and p=0.034).

In group II, there is no statistically significant change in the level of depression in the 2nd and 4th months, compared to the baseline. A statistically significant change is observed at the third month compared to the beginning (p=0.048).

It is observed that there is a statistically significant change in the depression level in group III in the 2nd, 3rd, and 4th months compared to the baseline (p=0.006, p=0.003, and p=0.004).

In the 3rd month, there was a statistically significant change in BDI scores in all three groups at baseline. However, in group II, there is no significant change observed in the fourth month compared to the beginning.

It is observed that there is a statistically significant change in the Beck Depression scoring in group I and group III in the 4th month, compared to the beginning. Wet cupping therapy and drug therapy appear to be effective methods in reducing the depression level of migraine-without-aura patients.

Table 3 shows how WHOQOL-8 scores changed over time in three different groups. The baseline mean WHOQOL-8 score was 24.50 in group I, 24.64 in group II, and 27.04 in group III. There is no statistically significant difference in baseline data between groups (p=0.155). In this case, comparisons can be made between the three groups.

WHOQOL-8 Scale

In group I, there is a statistically significant change (increase) in the WHOQOL-8 scale score in the 2nd, 3rd, and 4th months compared to the baseline.

In group II, there was a statistically significant change in the WHOQOL-8 scale score at the 3rd and 4th months compared to the beginning. There is no statistically significant change in the second month compared to the beginning (p=0.585).

In group III, no statistically significant change was observed in the WHOQOL-8 scale at the 2nd, 3rd, and 4th months compared to baseline.

It was observed that the change in the WHOQOL-8 scale score, that is the increase in the individuals' quality of life level, was statistically significant in the wet and dry cupping therapy groups. This shows that improving the quality of life of migraine sufferers is possible with wet cupping and dry cupping treatments over time.

Discussion

There are two main types of migraine: migraine with aura and migraine without aura. During migraine attacks, it is clinically important to distinguish whether migraine is with or without aura. The most common type is migraine without aura. When the literature is examined, studies investigating the effects of cupping therapy on migraine do not take the type of migraine into account; that is, no specific study has been conducted on specific migraine types, such as with or without aura. The most important feature of our study that reveals its originality is that only patients with migraine without aura were included in all three groups.

In a study involving 128 participants at a university in Jeddah from 2013 to 2015, individuals received wet cupping therapy once a month for 4 months (12). According to the results of this study, it was determined that cupping therapy reduced the VAS score and increased the quality of life in people with migraines. In our study, data similar to the results were obtained. It has been observed that wet cupping therapy significantly increases the quality of life in migraine without aura patients, as of the 2nd month, and dry cupping therapy significantly increases the quality of life in this patient group, as of the 3rd month. It appears that there is no statistically significant increase in the WHOQOL-8 scale score in patients, in the medication group. According to these results, wet cupping therapy can be considered the most effective method to improve the quality of life in patients with migraine without aura.

In a study conducted at Karabük, another hospital between 2016 and 2018, cupping therapy, which was applied to 5 points on the back every month, was terminated in the first group of patients and was continued as needed in the other group of patients (13). VAS and MIDAS scores of patients in both groups were evaluated at baseline, 6th month,

Table 3. WHOQOL-8 change analysis

		Group I			Group II			Group III			p	
WHOQOL-8												
Starting date	M ± SD	24.50	±	5.62	24.64	±	5.31	27.04	±	3.67	0.155	K
	Median	24.00			25.00			27.00				
Change compared to the start												
2nd month change	M ± SD	1.83	±	4.51	0.72	±	4.24	0.42	±	1.18	0.217	K
	Median	1.50			0.00			0.00				
In group change p		**0.043**		W	0.585		W	0.071		W		
3rd month change	M ± SD	2.67	±	4.99	2.92	±	4.18	0.27	±	0.77	**0.018**	K
	Median	2.00			3.00			0.00				
In group change p		**0.025**		W	**0.004**		W	0.098		W		
4th month change	M ± SD	3.25	±	4.46	3.36	±	5.51	-1.63	±	6.81	**0.009**	K
	Median	3.00			4.00			0.00				
In group change p		**0.002**		W	**0.010**		W	0.924		W		

K: Kruskal-wallis ((Mann-Whitney U test), W: Wilcoxon test, SD: Standard deviation, M: Mean, WHOQOL-8: World Health Organization Quality of Life Scale – 8-

and 12th month. As a result of the study, it was revealed that the VAS of the patient group that continued wet cupping therapy decreased significantly compared to the initial measurements of that group. As a result of the study, it was concluded that continuing cupping therapy would have positive effects on patients. This result is also supported by our study. Attack frequency, attack severity, attack duration, depression, and anxiety levels show a statistically significant decrease in the wet cupping therapy group. It was found that attack frequency and attack severity decreased in the dry cupping therapy group.

The predominance of female participants in our study can be explained by the fact that migraine disease is 2-3 times more common in women than in men (14); additionally, women have longer migraine attacks and need more time for the attack to pass. This means that women have more migraine problems both in severity and frequency and that they seek treatment more than men.

It is known that hormonal changes in women, especially changes in estrogen levels during and before menstruation, trigger migraines. In our study, patients who had migraine attacks during menstruation or whose migraine attacks were related to menstruation were not included. In this way, since women's menstruation-related changes are not included in the study, the relationships between hormones and migraine, as well as the effect of cupping therapy on hormonal migraine attacks, should be specifically studied.

Wet cupping therapy significantly increases the quality of life of healthy individuals. According to the results from 290 people in Iran, where the Quality of Life Scale was applied before and one month after cupping therapy to the Kahil point, cupping therapy significantly improves the quality of life of healthy people (15). In our study, it was observed that both wet and dry cupping therapy improved the quality of life in patients with migraine without aura. It has been observed that drug treatment does not affect patients with migraine without aura after four months of treatment compared to baseline. It was observed that wet cupping therapy statistically increased the quality of life in the 2nd month compared to the beginning, while dry cupping therapy increased it in the 3rd month.

A meta-analysis of 16 articles published in 2014 showed that cupping therapy reduced the level of acute and chronic pain. This result is consistent with our study. Both wet and dry cupping therapy also reduce the severity of migraine attacks. Again, as a result of this meta-analysis, cupping therapy was found to be more effective than the untreated control group, and the hot application group. In all studies examined, it is noted that the only negative aspect of cupping therapy is ecchymosis in the area where cupping is applied, and this ecchymosis passes within 3-5 days (16). In our study, no complications were encountered in 24 patients who received wet cupping therapy and 25 patients who received dry cupping therapy over 6 sessions.

Our study shows that wet cupping therapy, statistically significantly reduces the anxiety and depression levels of patients with migraine without aura at the beginning of the 3rd month. It was observed that the quality of life started to increase significantly in a statistical sense from the second month.

Dry cupping therapy has been observed to reduce depression in patients with migraine without aura in the 3rd month, but not in the 4th month, and it does not statistically reduce anxiety. It increases the quality of life in a statistically significant manner by the third month. The positive effect of dry cupping therapy on anxiety was not found in our study.

In the prophylactic drug treatment group, drug treatment was observed to reduce depression significantly statistically in the second month. It was observed that prophylactic drug treatment reduced anxiety in the 2nd and 3rd months, but did not significantly reduce it in the 4th month. Similarly, it was observed that the quality of life of the patients did not significantly increase in patients receiving prophylactic drugs.

In our study, wet and dry cupping therapy was applied not only to the interscapular and C7 point, but also to the OP point (Figure 1), which is recommended for use in migraine disease. Applying the treatment to the head area in wet and dry cupping therapy, determining the interval of the first 4 sessions as 15 days and the subsequent sessions as one month, and reaching statistically significant results in many parameters in cupping therapy shows the originality of the study. The data that are meaningful to compare between groups are the data on attack duration, BDI, and WHOQOL-8 scale. It was observed that while the wet cupping therapy and prophylactic drug treatment group caused a statistically significant reduction in the duration of the attack, starting from the 3rd month and continuing its effect in the 4th month, the dry cupping group had no continued effectiveness in reducing the duration of the attack. Wet cupping therapy and prophylactic drug therapy are superior to dry cupping therapy in reducing the duration of attacks in patients with migraine without aura. It is understood from the results of our study, that wet cupping therapy and prophylactic drug treatment are effective in reducing the level of depression in patients with migraine without aura. No continuing effect of dry cupping therapy on depression was observed at 4 months. It is understood that wet cupping therapy and drug therapy are superior to dry cupping therapy in reducing depression levels. When making a comparison between the drug group and wet cupping therapy, it is important to note that the major tricyclic antidepressant amitriptyline is used in the drug group, which has a positive discrimination at this point.

The evaluation of the quality of life in 3 different groups included in the study revealed that wet cupping therapy increased the quality of life of individuals the most byin the 2nd month, dry cupping therapy increased their quality of life in the 3rd month, and the significant results continued at the end of the 4th month. It was observed, that the quality of life of the patients did not increase significantly in the prophylactic drug treatment group. It has been understood that wet cupping therapy is superior to dry cupping therapy and prophylactic drug treatment, in improving the quality of life of migraine without aura patients.

Wet and dry cupping therapy is a non-invasive, cheap, and easily applied treatment method that has been used for treatment and health protection since ancient times and has recently become popular again. Although positive results have been observed in studies conducted on acute migraine attacks (17), our study shows that wet and dry cupping therapy can be used as an effective treatment method. It is effective in reducing the severity and frequency of attacks, reducing the level of

depression, and increasing the quality of life for people with chronic migraine disease. A prophylactic migraine medication is expected to reduce the frequency of migraine attacks by at least 50%. It is understood from other studies in the literature, and this current study, that this result has been successfully achieved in wet and dry cupping therapy.

Study Limitations

This study was performed only on patients with migraines without aura. This situation is a limitation of this study. There is a need for further studies on the effect of cupping therapy on migraine with aura.

The study's total number of patients is limited to 75, and the age interval is between 18 and 58 years. However, it is recommended that studies be conducted with larger numbers of patients and in more specific age groups.

Conclusion

Our study results indicate that wet and dry cupping therapy can be used as a prophylactic method in patients with migraine without aura. It is observed that wet cupping therapy causes a statistically significant decrease in the anxiety and depression levels of the patients, and increases the quality of life. Dry cupping therapy has been observed to improve the quality of life of patients. While wet cupping therapy, dry cupping therapy, and prophylactic drug therapy are preferred, the effectiveness of these methods mentioned in our study, their side effects, and cost should be evaluated, and the method that will best benefit the patient should be preferred.

Ethics

Ethics Committee Approval: The study was approved by the GETAT Clinical Research Ethics Committee (approval number: 2024-052, date: 30.04.2024).

Informed Consent: All participants read and signed the informed consent form.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 279-85
DOI: 10.4274/imj.galenos.2025.57936

The Effects of Different Treatment Procedures Applied to Trigger Finger on Recurrence

Bedrettin Akar[1], Ahmet Doğan[2], Mehmet Bülent Balıoğlu[3], Yusuf Öztürkmen[4], Mehmet Albayrak[5], Erhan Şükür[6], Fatih Uğur[7]

[1]Yenikent State Hospital, Clinic of Orthopedics and Traumatology, Sakarya, Türkiye
[2]Private Clinic, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Türkiye
[5]Rumeli University Faculty of Medicine, Department of Orthopedics and Traumatology, İstanbul, Türkiye
[6]Biruni University Faculty of Medicine, Deparment of Orthopedics and Traumatology, İstanbul, Türkiye
[7]Kastamonu University Faculty of Medicine, Deparment of Orthopedics and Traumatology, Kastamonu, Türkiye

ABSTRACT

Introduction: To investigate the effects of two different treatment methods on the recurrence rates within one year and on clinical and functional outcomes in patients with trigger finger (TF) complaints.

Methods: The files of 137 patients diagnosed with TF at our clinic between 2018 and 2022, who received two different treatments administered by two different physicians, were retrospectively reviewed. After applying the exclusion criteria, the study included 111 patients, of whom 66 underwent surgical release and were designated as group I, and 55 received steroid injections and were designated as group II. The Wolfe grading system was used to evaluate the severity of TF, and the Visual Analog Scale was employed to measure pain levels. Clinical and functional outcomes were assessed at the third and sixth months, and one year after treatment to evaluate the effect of each procedure on the development of recurrence.

Results: In group II, the distribution of grade II and grade IIIa recurrence in the first three and six months was found to be statistically significantly higher than in group I (p=0.005 and p=0.045, respectively). In the first year, the distribution of grade II, grade IIIa, and grade IIIb recurrences in group II was also significantly higher statistically compared to group I (p=0.007). No statistically significant difference was observed between group I and group II in terms of the distribution of improvement from baseline to the third and sixth months after treatment (p=0.295 and p=0.118, respectively). All patients in both group I and group II who experienced recurrence were treated surgically.

Conclusion: Although the ease of application and rapid effectiveness of steroid injection may appear advantageous compared to surgical methods in the treatment of TF, the high recurrence rates after the first six months negatively affect the potential for sustained success with steroid injection treatment.

Keywords: Trigger finger, surgical treatment, tendons, methylprednisolone acetate, rehabilitation, conservative treatment

Introduction

Trigger finger (TF), also known as stenosing tenosynovitis, is one of the most common hand disorders, affecting approximately 2-3% of the global population. Its annual incidence in the general population is 30 cases per 100,000, and its lifetime prevalence is 2.8%, with a particular frequency among women in their 50s and 60s (1,2). It is more commonly observed in the dominant hand, predominantly affecting the thumb, third, and fourth digits. Fibrous bands called pulleys, located along the flexor tendon sheath in the hand, anchor the flexor tendons tightly to the phalanges during finger flexion and extension movements (2). Each finger has five distinct pulley regions extending distally from the metacarpophalangeal (MP) joint level on the palmar surface. TF develops as a result of stenosis caused by inflammation of the A1 pulley located at the MP joint level. This condition arises due to the disparity between the thickened and narrowed sheath and the flexor tendon. There is non-specific causative agent in the etiology of TF. Multiple etiological factors are considered to play a role.

Address for Correspondence: Bedrettin Akar MD, Yenikent State Hospital, Clinic of Orthopedics and Traumatology, Sakarya, Türkiye
E-mail: drbedrettin@gmail.com **ORCID ID:** orcid.org/0000-0001-7461-1777

Cite this article as: Akar B, Doğan A, Balıoğlu MB, Öztürkmen Y, Albayrak M, Şükür E, et al. The effects of different treatment procedures applied to trigger finger on recurrence. İstanbul Med J. 2025; 26(4): 279-85

Received: 27.07.2025
Accepted: 14.09.2025
Publication Date: 12.11.2025

Risk factors for TF include diabetes, rheumatoid arthritis, strenuous hand activities, and female sex. It is observed with up to six times the frequency in women, and is most common during the fifth and sixth decades of life (3,4). In the pathophysiology of TF, the tendon experiences friction due to the significant degeneration of the fibrocartilaginous surface within the stenotic A1 pulley, which impedes tendon gliding. This friction leads to nodular changes in the tendon and inflammation manifested as hypervascularity in the flexor tendon (3-5). Over time, smooth motion of the flexor tendon within the A1 pulley becomes increasingly difficult. When the finger is flexed and the thickened nodule passes through the tight pulley, a catching or snapping sensation occurs, which is often painful. In severe cases of TF, the finger may become locked in a flexed position. Patients may occasionally need to use their other hand to manually extend the affected finger or thumb (5,6). Treatment options range from conservative methods such as splinting to corticosteroid injections: percutaneous release, or open surgical release. There is no definitive guideline for the treatment algorithm. The classic presentation of TF with clicking and locking is usually sufficient for diagnosis, however, patients may present with pain and swelling over the affected flexor sheath due to the acute symptom onset and avoidance of finger movement. Imaging plays no role in diagnosis (6-8).

In this study, we aimed to investigate the effect of two different treatment methods on recurrence development within one year in patients with TF complaints, based on clinical and functional outcome evaluations.

Methods

A retrospective review was conducted on the medical records of 137 patients diagnosed with TF who presented to our clinic between 2018 and 2022. The study was approved by the Sakarya University Non-Interventional Ethics Committee (approval number: E-71522473-050.01.04-216230-23, date: 31.01.2023). Patients who did not attend regular follow-ups, those with renal failure undergoing dialysis, those receiving oncological treatment, and those with coexisting Dupuytren's contracture in the hand were excluded from the study. Following the application of exclusion criteria, 111 patients were included in the analysis. Two treatment methods were applied by two physicians. A total of 66 patients who underwent surgical release under local anesthesia were designated as group I, and 55 patients who received a steroid injection (methylprednisolone acetate) into the A1 pulley were designated as group II. The severity of TF in patients was categorized using the Wolfe grading system.

Surgical procedures were performed under operating room conditions without the use of a tourniquet. After the subcutaneous administration of a local anesthetic (prilocaine hydrochloride) to the incision site, a 2-cm transverse incision was made, using the midpoint of the pulley as a reference. Care was taken to preserve vascular structures as the incision was deepened subcutaneously to reach the pulley. The pulley was released with a longitudinal incision extending proximally, and distally. Following the release, the tendons were assessed for any residual catching by performing flexion and extension movements of the finger (Figure 1). Upon confirmation of adequate release, and absence of locking, the anatomical layers were closed, and an elastic bandage was applied. Postoperatively, patients received a one-week course of oral antibiotics and non-steroidal anti-inflammatory drug therapy. Passive exercises were initiated during the first postoperative week, followed by active exercises over the next two weeks. Sutures were removed on postoperative day 15.

In the steroid injection procedure, a mixture of 1 cc of long-acting steroid (methylprednisolone acetate) and 1 cc of local anesthetic, was administered over the pulley and tendon sheath. The steroid injection was administered only once by two physicians using a similar technique. No ultrasound or similar devices were used during the procedure; instead, an insulin injection was administered manually, using the midline of the pulley. These procedures were carried out under outpatient clinic conditions. Following both treatment modalities, the Wolfe grading system was used to assess the severity of TF based on flexion-extension movements of the fingers, while the Visual Analog Scale (VAS) was employed to evaluate pain levels. Clinical and functional outcomes were assessed at the third and sixth months, and one year after treatment in order to investigate the effect of the intervention on recurrence.

Statistical Analysis

In this study, statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package. In the evaluation of data, descriptive statistical methods (mean ± standard deviation) were used, and the distribution of variables was assessed using the Shapiro-Wilk normality test. For variables with a normal distribution, comparisons between two groups were made using the Independent Samples t-test. For the comparison of categorical data, the chi-square test and Fisher's exact test were used. Results were considered statistically significant at a p-value of <0.05.

Results

The mean age was 55.32±8.96 years for group I and 57.64±9.34 years for group II. The mean follow-up durations were 17.42±4.14 months for group I and 16.80±4.35 months for group II. Group I consisted of 66 patients (12 males and 54 females). In this group, 35 procedures were performed on the right extremity and 31 on the left. Group II included 55 patients, of whom 7 were male and 48 were female. In this group, 35 interventions were performed on the right side and 20 on the left (Table 1). In group I, 51 patients (77.27%) presented with TF in the first digit, while in group II, 43 patients (78.18%) had TF in the first digit. No statistically significant differences were observed between group I and group II in terms of mean age and sex distribution (p=0.167 and

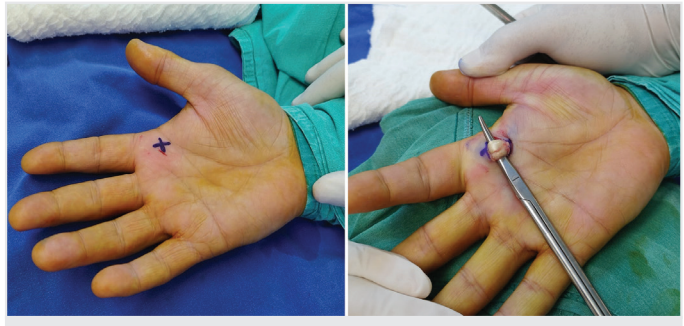

Figure 1. Trigger finger surgery (patient consent obtained)

p=0.412, respectively). Similarly, no statistically significant differences were identified in laterality or affected finger distribution between the groups (p=0.239 and p=0.920, respectively). The presence of comorbidities such as hypertension, vascular disease, chronic obstructive pulmonary disease, renal failure, heart disease, or rheumatoid arthritis showed no statistically significant differences between groups (p>0.05).

No statistically significant difference was observed between the groups in terms of the distribution of TF severity according to the Wolfe classification (p=0.965). However, in group II, the presence of grade II and grade IIIa recurrences at three and six months was significantly higher than in group I (p=0.005 and p=0.045, respectively). Similarly, during the first year, the distributions of grade II, grade IIIa, and grade IIIb recurrence in group II were significantly higher than in group I (p=0.007) (Table 2).

In group II, 8 patients (14.55%) showed no change and 4 patients (7.27%) had clinical worsening from pre-treatment to the one-year follow-up. These distributions were significantly higher than those in group I (p=0.001). No statistically significant difference was found between the groups regarding the distribution of clinical improvement from pre-treatment to the third and sixth months (p=0.295 and p=0.118, respectively). However, the number of patients with no change (n=8, 14.55%) or worsening (n=4, 7.27%) at the one-year mark was again significantly higher in group II than in group I (p=0.001) (Figure 2). All patients in both groups who experienced recurrence underwent surgical release (Table 3).

No statistically significant difference was found between the pre-treatment mean VAS scores of the groups (p=0.273). At the third month after treatment, the mean VAS score in group I was significantly higher than in group II (p=0.001). However, at six months, group I had significantly lower VAS scores than group II (p=0.001), and at one year, group I showed significantly lower VAS scores (p=0.0001) (Table 4).

A statistically significant change was observed between pre-treatment and post-treatment three-month, six-month, and one-year mean VAS scores in group I (p=0.0001). Pre-treatment VAS scores were significantly higher than scores at all post-treatment timepoints (p=0.0001). Three-month VAS scores were significantly lower than both six-month and one-year scores (p=0.0001). Six-month scores were significantly higher than one-year scores (p=0.0001). Similarly, a statistically significant

Table 1. Comparison of demographic characteristics

		Surgical release n=66		Steroid injection n=55		p
Age (years)		55.32±8.96		57.64±9.34		0.167*
Sex	Male	12	18.18%	7	12.73%	0.412⁺
	Female	54	81.82%	48	87.27%	
Affected side	Right	35	53.03%	35	63.64%	0.239⁺
	Left	31	46.97%	20	36.36%	
Affected finger	First digit	51	77.27%	43	78.18%	0.920⁺
	Second digit	7	10.61%	6	10.91%	
	Third digit	2	3.03%	1	1.82%	
	Fourth digit	5	7.58%	3	5.45%	
	Fifth digit	1	1.52%	2	3.64%	
Comorbidities	Absent	28	42.42%	33	60.00%	0.054⁺
	Present	38	57.58%	22	40.00%	
Hypertension	Absent	48	72.73%	41	74.55%	0.821⁺
	Present	18	27.27%	14	25.45%	
Diabetes	Absent	46	69.70%	49	89.09%	0.01⁺
	Present	20	30.30%	6	10.91%	
Vascular disease	Absent	64	96.97%	53	96.36%	0.998‡
	Present	2	3.03%	2	3.64%	
COPD	Absent	64	96.97%	55	100.00%	0.501‡
	Present	2	3.03%	0	0.00%	
Renal failure	Absent	61	92.42%	52	94.55%	0.640⁺
	Present	5	7.58%	3	5.45%	
Heart disease	Absent	63	95.45%	55	100.00%	0.250‡
	Present	3	4.55%	0	0.00%	
Rheumatoid arthritis	Absent	64	96.97%	50	90.91%	0.155⁺
	Present	2	3.03%	5	9.09%	

*Independent Samples t-test, ⁺Chi-square test, ‡Fisher's exact test
COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of recurrence rates between groups

		Surgical release n=66		Steroid injection n=55		p
Trigger finger severity (Wolfe classification)	Grade II	29	43.94%	24	43.64%	0.965+
	Grade IIIa	22	33.33%	18	32.73%	
	Grade IIIb	9	13.64%	9	16.36%	
	Grade IV	6	9.09%	4	7.27%	
Recurrence within three months	None	64	96.97%	43	78.18%	**0.005**+
	Grade II	2	3.03%	10	18.18%	
	Grade IIIa	0	0.00%	2	3.64%	
Recurrence within six months	None	63	95.45%	46	83.64%	**0.045**+
	Grade II	3	4.55%	5	9.09%	
	Grade IIIa	0	0.00%	4	7.27%	
Recurrence within one year	None	62	93.94%	39	70.91%	**0.007**+
	Grade II	3	4.55%	10	18.18%	
	Grade IIIa	1	1.52%	3	5.45%	
	Grade IIIb	0	0.00%	3	5.45%	

+Chi-square test

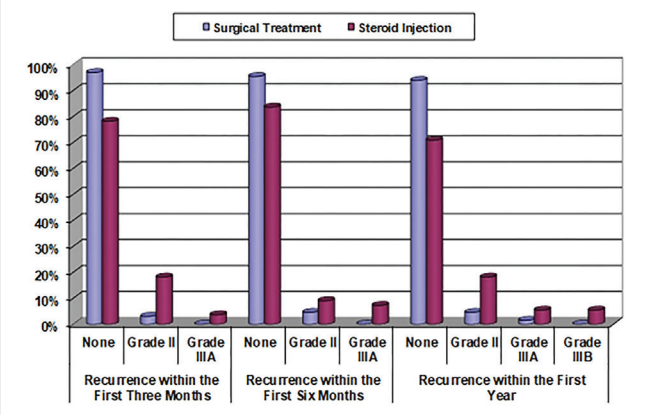

Figure 2. Comparison of recurrence rates within the first year

change was observed among all follow-up timepoints in group II (p=0.0001). Pre-treatment VAS scores were significantly higher than those at all post-treatment times (p=0.0001). While three-month scores were significantly lower than one-year scores (p=0.0001), there was no statistically significant difference between three-month and six-month scores (p=0.619). However, six-month scores were significantly lower than one-year scores (p=0.0001, Table 5).

The difference in VAS scores between pre-treatment and the three-month follow-up in group I was significantly lower than in group II (p=0.012). No statistically significant difference was found between the groups regarding the change in VAS scores from pre-treatment to the six-month follow-up (p=0.414) (Figure 3). However, the change from pre-treatment to the one-year follow-up was significantly greater in group I than in group II (p=0.0001) (Table 6).

Discussion

TF is a condition characterized by painful locking or catching of the fingers due to inflammation of the flexor tendon sheath, caused by various factors (9). During flexion and extension movements, the gliding motion of the flexor tendon becomes obstructed. TF has a prevalence of approximately 2.8% in the general population and up to 12% among patients with diabetes (9,10). Although it may be perceived as a simple condition, it can significantly impact daily life and functional capacity. Histological evaluation of the affected tissues suggests fibrocartilaginous metaplasia of the tendon sheath and the A1 pulley as a secondary response to inflammation. There are multiple treatment options for TF; however, determining the method that offers the highest clinical success and lowest recurrence rate remains a subject of debate (10,11). In our study, which examined the effect of two different treatment modalities on recurrence rates within one year, we observed that both methods yielded comparable clinical and functional outcomes at three and six months, with no significant difference in recurrence rates during this period. Nevertheless, after the six-month mark and within the first year, patients treated with steroid injections demonstrated a significant decline in clinical and functional outcomes, along with a notable increase in recurrence rates compared to the surgical group. We therefore conclude that surgical intervention should be the preferred method to achieve a durable and effective outcome in the treatment of TF.

Guillén Astete et al. (12) reported that steroid injections in grade II and III TF cases, achieved clinical and functional success rates of up to 70% in the early months, but recurrence rates increased significantly after 12 months. Emphasizing the importance of appropriate patient selection, the authors advocated for prompt surgical release in advanced-stage cases. In another study, Patrinely et al. (13) highlighted that the mixture of local anesthetic with steroid provided a painless and comfortable treatment option for TF, with high success rates. Gil et al. (14) stated that releasing the A1 pulley effectively reduced both the subjective and objective findings of TF and remains the reference procedure in its treatment. In addition, they reported that prophylactic antibiotic use in elective hand surgery cases was unnecessary. In our study, however,

Table 3. Comparison of improvement rates between groups

Improvement		Surgical release n=66		Steroid injection n=55		p
Pre-treatment to post-treatment month 3	No change	0	0.00%	1	1.82%	0.295+
	Improvement	66	100.00%	53	96.36%	
	Worsening	0	0.00%	1	1.82%	
Pre-treatment to post-treatment month 6	No change	0	0.00%	2	3.64%	0.118‡
	Improvement	66	100.00%	53	96.36%	
Pre-treatment to post-treatment year 1	No change	1	1.52%	8	14.55%	**0.001**+
	Improvement	65	98.48%	43	78.18%	
	Worsening	0	0.00%	4	7.27%	

+Chi-square test, ‡Fisher's exact test

Table 4. Comparison of VAS scores of groups by follow-up timepoints

VAS score		Surgical release n=66	Steroid injection n=55	p
Pre-treatment	Mean ± SD	7.76±0.77	7.93±0.74	0.273
	Median (IQR)	8 (7-8)	8 (7-8)	
Post-treatment month 3	Mean ± SD	1.89±0.81	1.64±1.25	**0.001**
	Median (IQR)	2 (1-2)	1 (1-2)	
Post-treatment month 6	Mean ± SD	1.38±0.92	1.78±1.27	**0.001**
	Median (IQR)	1 (1-2)	2 (1-2)	
Post-treatment year 1	Mean ± SD	0.73±1.44	3.33±2.49	**0.0001**
	Median (IQR)	0 (0-1)	2 (1-6)	
p‡		0.0001	0.0001	

†Mann-Whitney U test, ‡Friedman test
VAS: Visual Analog Scale, SD: Standard deviation, IQR: Interquartile range

Table 5. Multiple comparisons by follow-up timepoints in treatment groups using Dunn's multiple comparison test

Dunn's multiple comparison test	Surgical release n=66	Steroid injection n=55
Pre-treatment vs. post-treatment month 3	0.0001	0.0001
Pre-treatment vs. post-treatment month 6	0.0001	0.0001
Pre-treatment vs. post-treatment year1	0.0001	0.0001
Post-treatment month 3 vs. month 6	0.0001	0.619
Post-treatment month 3 vs. year 1	0.0001	0.0001
Post-treatment month 6 vs. year 1	0.0001	0.0001

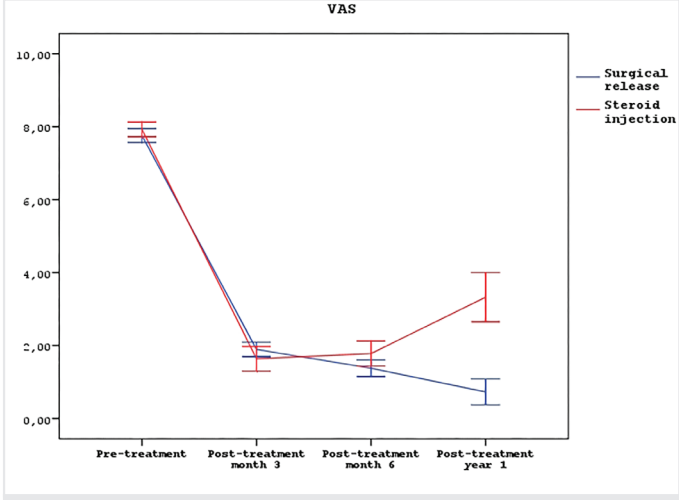

Figure 3. Graphical representation of changes in VAS scores over time by treatment group
VAS: Visual Analog Scale

patients who underwent surgery were prescribed a one-week course of oral antibiotics.

Mirza et al. (15) compared postoperative complications of open and endoscopic release techniques in TF surgery and found that both methods were effective, with comparable rates of minor postoperative complications. Pompeu et al. (16) concluded that in advanced cases of TF, steroid injections did not yield satisfactory clinical or functional outcomes and were ineffective against flexion contractures. They recommended prompt release of the A1 pulley in such cases and drew attention to the risk of permanent extension deficits after release. Effendi et al. (17) reported that while major complications after release surgery were rare, patients with poorly controlled diabetes might experience higher postoperative infection rates, which could potentially lead to severe wound complications and necrosis. In our study, no serious complications such as wound issues, infections, necrosis, or flexor tendon rupture were observed in diabetic patients. Notably, we

Table 6. Comparison of pre-treatment to follow-up differences in VAS scores between treatment groups

VAS score		Surgical release n=66	Steroid injection n=55	p†
Pre-treatment- post-treatment month 3 difference	Mean ±SD	5.86±1.14	6.29±1.4	**0.012**
	Median (IQR)	6 (5-7)	7 (6-7)	
Pre-treatment - post-treatment month 6 difference	Mean ± SD	6.38±1.11	6.15±1.48	0.414
	Median (IQR)	6.5 (6-7)	6 (6-7)	
Pre-treatment - post-treatment year 1 difference	Mean ± SD	7.03±1.38	4.6±2.72	**0.0001**
	Median (IQR)	7 (7-8)	5 (2-7)	

†Mann-Whitney U test
VAS: Visual Analog Scale, SD: Standard deviation, IQR: Interquartile range

observed that patients receiving steroid injections experienced less relief after six months, and their symptoms approached their pre-treatment levels. In a study involving 192 patients with and without diabetes, Stirling et al. (18) reported a high rate of patient satisfaction (96%) with surgical treatment for TF, and found comparable improvements in both groups. In another study, Koopman et al. (19) found a complication rate as high as 17% following surgical release for TF, but noted that it was clinically insignificant. Despite the complication rate, the authors emphasized that surgery should be the primary treatment choice due to its effectiveness in reducing recurrence. Çimen and Nami (20) stated that percutaneous release was a safe and successful method in TF surgery and that neither diabetes nor prior steroid injections affected clinical outcomes. In a study on the management of TF by orthopedic surgeons in Brazil, Silva et al. (21) found that steroid injections and non-steroidal anti-inflammatory drug therapy were typically used within the first month to three months. However, for persistent or recurrent cases after the third month, surgical release was preferred. Roberts et al. (22) investigated the efficacy of different steroid preparations in TF cases and found that patients treated with methylprednisolone required surgical release more frequently and earlier than those treated with triamcinolone or dexamethasone.

Study Limitations

This study has several limitations. First, the retrospective design and lack of randomization prior to treatment may limit the generalizability of the findings. Second, the subjective assessment of TF severity through physical examination introduces the possibility of measurement error. Third, the sample size may be insufficient to draw definitive conclusions. Therefore, future prospective studies involving a larger number of patients and a broader spectrum of comorbidities are warranted to address these limitations.

Conclusion

Although the simplicity and rapid effectiveness of steroid injection may provide clinical and functional results comparable to surgery in the first six months, the markedly higher recurrence rates beyond six months negatively affect the long-term and permanent success of this treatment method. Our study demonstrates that surgical treatment of TF results in significantly lower recurrence rates within the first year compared to treatment with steroid injection. We emphasize that surgical intervention should be considered a primary treatment option to achieve lasting and effective outcomes in TF management. We hope that this study will contribute to future research in the treatment of this condition, and believe that further studies including a greater number of patients and more variables are needed.

Ethics

Ethical Approval: The study was approved by the Sakarya University Non-Interventional Ethics Committee (approval number: E-71522473-050.01.04-216230-23, date: 31.01.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - B.A., Y.Ö., F.U.; Concept - B.A., A.D., M.A., E.Ş.; Design - B.A., A.D., M.B.B., Y.Ö., F.U.; Data Collection or Processing - B.A., M.B.B., M.A., E.Ş.; Analysis or Interpretation - B.A., F.U.; Literature Search - B.A., A.D., M.B.B., M.A., F.U.; Writing - B.A., A.D., Y.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 286-92
DOI: 10.4274/imj.galenos.2025.30676

The Relationship of Aortic Knob Width and Prognosis in COVID-19 Patients

Mehmet Semih Çakır[1], Mehmet Sait Altıntaş[2]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Cardiology, İstanbul, Türkiye

ABSTRACT

Introduction: To investigate the relationship between aortic knob width (AKW) and prognosis in patients hospitalized due to coronavirus disease-2019 (COVID-19), and to determine whether AKW can be used as a predictor of in-hospital mortality.

Methods: This cross-sectional study included 222 patients who were hospitalized with COVID-19 following emergency department admission. Based on the clinical outcome, patients were categorized into two groups: those who died during hospitalization (group 1, n=64) and those who survived (group 2, n=158). Demographic, clinical, laboratory, and radiological data were collected retrospectively. AKW was measured on chest radiographs, and its association with in-hospital mortality was assessed through multivariate logistic regression and receiver operating characteristic curve analysis.

Results: AKW was significantly higher in deceased patients compared to survivors (45.1±8.8 mm vs. 36.7±6.7 mm; p<0.001). A cut-off value of 40 mm for AKW predicted in-hospital mortality with 76.6% sensitivity and 70.3% specificity. AKW was found to be an independent predictor of in-hospital mortality (odds ratio: 1.196, 95% confidence interval: 1.106-1.293, p<0.001). AKW showed significant correlations with age, inflammatory markers (C-reactive protein, ferritin, procalcitonin), and clinical severity parameters, such as oxygen saturation and respiratory rate.

Conclusion: AKW measured on chest X-rays at the time of admission is a non-invasive and accessible prognostic marker in hospitalized COVID-19 patients. Values above 40 mm may indicate increased mortality risk, and these patients should be monitored more closely during hospitalization.

Keywords: Aortic knob width, COVID-19, prognosis, mortality, chest radiograph

Introduction

The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which has been defined as causing SARS since December 2019, has affected the whole world and continues to affect it (1). The World Health Organization has stated that it will continue its efforts to make an impact globally (2). In Covid-positive patients, simple symptoms such as fever, fatigue, dry cough, headache, and diarrhea can be observed, as well as acute respiratory distress syndrome (ARDS) and related cardiovascular shock. Disruptions in hematologic and immune system functions are key contributors to both the development and progression of the disease (3). Some cases may result in death despite treatment (3,4). Advanced age, the presence of comorbid conditions, and immunodeficiency are all associated with increased risks of morbidity and mortality (5). For this reason, it is important to make the diagnosis of coronavirus disease-2019 (COVID-19), predict the prognosis of the patients at the time of application, and determine the severity of the disease.

The aortic knob is a contour of the aortic arch and can be easily visualized on a chest radiograph. Dilatation of the aorta, which undergoes various changes with normal aging, has also been associated with atherosclerotic changes such as enlargement and calcification of the aortic knob (6). Studies have shown that aortic knob width (AKW) is associated with target organ damage in many diseases, especially in hypertension and coronary artery disease, (7-9). This study examined the relationship between AKW and prognosis in individuals hospitalized for COVID-19, based on the effects of multiple comorbidities on mortality and morbidity. Additionally, the correlation of this relationship with parameters determining the severity of the disease, as well as immunological and hematological parameters, was evaluated in this study.

Methods

Subjects

Our study was designed as a cross-sectional study and included 222 patients (121 males, 101 females, mean age: 60.0±16.6 years) who

Address for Correspondence: Mehmet Semih Çakır Asst. Prof., MD, İstanbul University, İstanbul Faculty of Medicine, Department of Radiology, İstanbul, Türkiye
E-mail: mehmetsemihcakir@gmail.com **ORCID ID:** orcid.org/0000-0002-7072-5985

Cite this article as: Çakır MS, Altıntaş MS. The relationship of aortic knob width and prognosis in COVID-19 patients. İstanbul Med J. 2025; 26(4): 286-92

Received: 26.07.2025
Accepted: 30.09.2025
Publication Date: 12.11.2025

applied to the emergency department with various complaints such as fever, cough, shortness of breath, and fatigue. Patients were hospitalized as a result of the examinations, and it was decided that they would be followed up and treated. Histories of the patients were taken, physical examinations were performed, and their information was recorded. The acute and chronic diseases of the patients, as well as the drug treatments they used, were recorded. Those with malignancy, rheumatological diseases, and chronic liver disease were identified as having systemic disease, and recorded. Temperatures of all patients were measured, and respiratory rates, systolic-diastolic blood pressures, pulses, and fingertip oxygen saturations were recorded by pulse oximetry. Venous blood samples were taken from all patients, and hemogram, D-dimer, alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, lactate dehydrogenase (LDH), C-reactive protein (CRP), troponin, ferritin, and procalcitonin values were measured at the time of admission to the hospital. These values were also measured during follow-up in individuals who were recommended to be hospitalized. In addition to hemogram parameters, neutrophil-lymphocyte ratio, and systemic inflammatory index (SII) were calculated. SII was found as multiplying the neutrophil to lymphocyte ratio with the platelet count.

Chest X-ray and Pulmonary Thorax Tomography

In posteroanterior imaging, AC radiography and lung tomography were performed on all patients. Chest radiographs were evaluated by a physician who was unaware of the patient's clinical information. The width of the aortic knob was assessed by measuring the maximum transverse diameter along the horizontal line extending from the lateral border of the trachea to the lateral wall of the aortic knob.

Information about the patient's pulmonary involvement was obtained from pulmonary tomography.

COVID-19 Diagnosis and Hospitalization Indication

The diagnostic criteria of the Turkish Ministry of Health National Science Committee were used as the COVID-19 diagnostic criteria for the patients. A confirmed positive diagnosis was established in individuals presenting with at least one symptom-such as fever, cough, dyspnea, sore throat, headache, myalgia, diarrhea, or loss of taste or smell-unattributable to other known conditions, alongside either a history of recent travel to a high-risk area within the preceding 14 days, close contact with a confirmed COVID-19 case during that period, or a positive SARS-CoV-2 result via molecular testing. Individuals diagnosed with severe acute respiratory infections-characterized by fever, cough, dyspnea, tachypnea, hypoxemia, hypotension, altered consciousness, and common radiological findings on lung imaging in patients with an acute respiratory tract infection that developed within the last 14 days-were required hospitalization for follow-up. Patients who required respiratory support or mechanical ventilation due to respiratory failure, developed cardiovascular shock and multiple organ failure, and had neurological symptoms, especially loss of consciousness due to desaturation, were monitored in the intensive care unit. The number of days the patients were hospitalized was recorded. The medication administered during the hospitalization was also recorded. All treatments applied to patients with hospitalization indications were administered by considering the treatment plan of the National Science Committee of the Turkish Ministry of Health (10). Also, the management of patients diagnosed with severe pneumonia, ARDS, sepsis, and septic shock during diagnosis and follow-up was carried out in accordance with the guidelines of the Ministry of Health of the Republic of Türkiye (11).

Out of 222 patients who were admitted to the hospital due to severe pneumonia, ARDS, sepsis, septic shock, and desaturation, 64 died. The study participants were divided into two groups: group 1, which consisted of 64 patients who resulted in death (mean age: 38 males, 69.2±16.2 years), and group 2, which consisted of 158 patients who did not result in death (83 males, 56.3±15.4 years).

An informed consent form was signed by the patients participating in the study, and the relatives of the individuals who were not in a position to give consent. The study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 46, date: 11.02.2022).

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0. Continuous variables were shown as mean ± standard deviation if normally distributed, and as median (25^{th}-75^{th} percentiles) if not. Categorical variables were presented as counts (n) and percentages (%). The Kolmogorov-Smirnov test was used to check if the numerical data had a normal distribution. Comparisons of continuous variables in two independent groups were made using the independent samples t-test and Mann-Whitney U test depending on the distributional characteristics of the parameters. Spearman's correlation analysis was used to evaluate the relationship between AKW and several other parameters. To assess the independent contribution of each variable, we performed a multiple logistic regression analysis that included all clinical variables with a $p<0.05$ in the univariate analysis. Hosmer and Lemeshow tests were performed to choose the best regression model. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed individually. To determine the AKW cut-off with optimal sensitivity and specificity for predicting mortality, receiver operating characteristic (ROC) curve analysis was employed. A p-value below 0.05 was regarded as statistically significant.

Regression analysis was performed to evaluate the independent effects on in-hospital mortality of demographic characteristics, admission physical examination findings, and laboratory findings. All variables that reached statistical significance ($p<0.05$) in the univariate analysis were included in the multiple logistic regression model. OR and 95% CI were calculated. ROC curve analysis was used to calculate the AKW value, which predicts in-hospital mortality with the best specificity and sensitivity.

Results

Group 1 had significantly older age and longer hospitalization compared to group 2 when demographic variables were evaluated. While gender, number of vaccinated patients, systolic-diastolic blood pressure was similar between the groups, fever, pulse and respiratory rate were significantly higher in group 1 compared to group 2. Oxygen

saturation was markedly reduced in group 1 relative to group 2. When the existing diseases of the individuals were compared, the presence of hypertension, coronary artery disease, kidney failure, heart failure, and systemic diseases was significantly higher in group 1 than in group 2 (Table 1).

AKW was significantly higher in group 1 compared to group 2 (45.1±8.8 mm vs. 36.7±6.7; p<0.001).

When laboratory values were compared, glucose, urea, creatinine, ALT, AST, LDH, CRP, ferritin, and D-dimer were significantly higher in group 1 compared to group 2. Procalcitonin and troponin values were similar between groups (Table 2). Among the hemogram parameters, white blood cells (WBC), hemoglobin, neutrophil, neutrophil to lymphocyte ratio, and SII were significantly higher in group 1 than group 2, while the monocyte value was significantly lower in group 1 compared to group 2. Lymphocyte and platelet values were similar between the groups (Table 1).

Pearson's correlation analysis showed a significant positive correlation with AKW and age, length of hospital stays, respiratory rate, heart rate,

Table 1. Demographic, laboratory features, hematological parameters, prognostic nutritional indices, systemic inflamatory indices of the groups

	Group 1 (n=64)	Group 2 (n=158)	p
Age (years)	69.2±16.2	56.4±15.4	<0.001
Gender (M,n)	38	83	0.355
Hospital stay duration (day)	17.4±11.5	9.1±6.5	<0.001
Temperature (ºC)	37.4±0.99	36.9±0.71	<0.001
Oxygen saturation (paO_2)	86.7±8.1	94.3±4.3	<0.001
Hypertension (n)	45	65	<0.001
Diabetes mellitus (n)	28	51	0.089
Coronary artery disease (n)	19	26	0.027
CHF (n)	21	18	<0.001
COPD (n)	8	16	0.607
CRF (n)	21	21	0.001
Vaccinated (n)	5	12	0.956
Systolic blood pressure (mmHg)	134.5±39.7	131.3±23.2	0.461
Diastolic blood pressure (mmHg)	77.5±17.1	78.3±12.7	0.684
Heart rate (beat/min)	103.9±14.6	95.2±13.0	<0.001
Respiratory rate (breath/min)	19.9±6.9	16.2±4.2	<0.001
Glucose (mg/Dl)	185.8±94.4	140.0±68.4	<0.001
Urea (mg/dL)	82.9±56.1	42.2±35.1	<0.001
Creatinine (mg/dL)	1.63±1.45	1.11±1.10	0.013
ALT (U/L)	87.8±179.8	37.2±65.0	0.003
AST(U/L)	168.7±448.3	38.7±54.7	0.023
LDH (U/L)	649.5±664.2	275.6±170.1	<0.001
CRP (mg/L)	144.3±94.9	34.7±66.4	<0.001
Procalcitonin	5.7±39.7	4.2±11.5	0.772
Ferritin	1859.3±4115.8	271.0±405.1	<0.001
D-dimer (mg/L)	3.98±5.35	1.85±3.97	0.001
Troponin I (pg/mL)	12.6±46.1	23.8±131.4	0.513
WBC ($x10^9$/L)	13.48±10.38	7.89±4.04	<0.001
Platelet ($x10^9$/L)	222.7±106.6	229.1 ± 86.7	0.640
Hemoglobin (g/Dl)	10.9±2.5	12.5±2.3	<0.001
Lymphocythe ($x10^9$/L)	1.84±0.79	1.73±2.34	0.873
Neutrophil ($x10^9$/L)	11.0±7.6	6.80±9.78	0.002
Neutrophil-to-lymphocyte ratio	21.33±23.70	6.23±10.60	<0.001
SII	4541.5±4872.7	1373.1±2494.0	<0.001
AKW (mm)	45.1±8.8	36.7±6.7	<0.001

CFH: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, AST: Aspartat transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cells, SII: Systemic inflamatory index, AKW: Aortic knob width

procalcitonin, CRP, ferritin, D-dimer, neutrophil to lymphocyte ratio, and SII (Table 2). There was a significant negative correlation between fingertip oxygen saturation and the variable of interest (Table 2).

In-hospital mortality-related factors identified through univariate and multivariate logistic regression analyses are detailed in Table 3. It was found to be predictive for in-hospital mortality in univariate analyses. Multivariate logistic regression was used to identify independent predictors of in-hospital mortality, utilizing variables that showed significance in univariate analyses. According to the multivariate logistic regression analysis, hypertension (OR =3.729, 95% CI: 1.194-11.645, p=0.023), low oxygen saturation (OR =0.904, 95% CI: 0.835-0.979, p=0.013), elevated LDH levels (OR =1.003, 95% CI: 1.000-1.005, p=0.020), increased ferritin (OR =1.001, 95% CI: 1.000-1.002, p=0.008), and greater AKW (OR =1.196, 95% CI: 1.106-1.293, p<0.001) were found to be independently associated with higher in-hospital mortality. ROC analysis showed that the area under the curve for AKW in predicting in-hospital mortality was 0.822 (95% CI: 0.758-0.886, p<0.001) (Figure 1). The cut-off value for AKW, which predicts in-hospital mortality, was 40.0 mm with a sensitivity of 76.6% and a specificity of 70.3%.

Table 2. Pearson's correlation analysis between AKW and several parameters

	rho	p
Oxygen saturation	-0.35	<0.001
Respiratory rate	0.35	<0.001
Heart rate	0.27	<0.001
C-reactive protein	0.35	<0.001
Procalcitonin	0.32	<0.001
D-dimer	0.34	<0.001
Ferritin	0.27	<0.001
Neutr-to-lymphocyte	0.37	<0.001
SII	0.34	<0.001

SII: Systemic inflamatory index, AKW: Aortic knob width.

Discussion

The main result of our study is that AKW, which can be easily measured on a posteroanterior chest X-ray, is associated with end-organ damage in various patient groups in previous studies. AKW is closely associated with mortality in COVID-19 patients requiring hospitalization. It is also closely linked to lab findings that reflect disease severity and to several markers of inflammation.

The structural and physical properties of the aortic wall change with age, and it loses its normal structure and function to certain degrees. It has been shown that the increase in aortic knob diameter is associated with age, body surface area, and gender, with a particularly strong association with hypertension. It has been stated that AKW may be an important indicator of the generalized atherosclerotic process due to its close relationship with coronary artery calcification and Framingham risk score (12,13). It was thought to be associated with target organ damage (14).

Individuals with severe COVID-19 are high-risk patients and often present with a high heart rate, low oxygen saturation, and a clinical picture of infiltrates of more than 50% of the lung on imaging (15). It is known that approximately 25% of patients who need to be hospitalized due to COVID-19 require intensive care (16,17). In serious COVID-19 cases, common complaints like fever, cough, sore throat, and breathing difficulties can worsen over time, leading to conditions such as ARDS,

Table 3. Univariate and multivariate regression analysis showing the parameters related with in-hospital mortality

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.057	1.034-1.080	<0.001			
Hypertension	3.389	1.818-6.317	<0.001	3.729	1.194-11.645	0.023
CAD	2.144	1.084-4.237	0.028			
CHF	3.889	1.897-7.972	<0.001			
CRF	3.186	1.590-6.385	0.001			
Saturation	0.816	0.764-0.871	<0.001	0.904	0.835-0.979	0.013
Heart rate	1.049	1.024-1.074	<0.001			
Glucose	1.007	1.003-1.011	<0.001			
Creatinin	1.361	1.076-1.723	0.010			
LDH	1.005	1.003-1.008	<0.001	1.003	1.000-1.005	0.020
CRP	1.012	1.008-1.016	<0.001			
Ferritin	1.002	1.001-1.003	<0.001	1.001	1.000-1.002	0.008
D-dimer	1.106	1.028-1.190	0.007			
WBC	1.168	1.094-1.248	<0.001	1.099	0.994-1.215	0.064
Hemoglobin	0.757	0.666-0.861	<0.001			
AKW	1.177	1.117-1.239	<0.001	1.196	1.106-1.293	<0.001

CAD: Coronary artery disease, CFH: Congestive heart failure, CRF: Chronic renal failure, AST: Aspartat transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cells, SII: Systemic inflamatory index, AKW: Aortic knob width, CI: Confidance interval, OR: Odds ratio

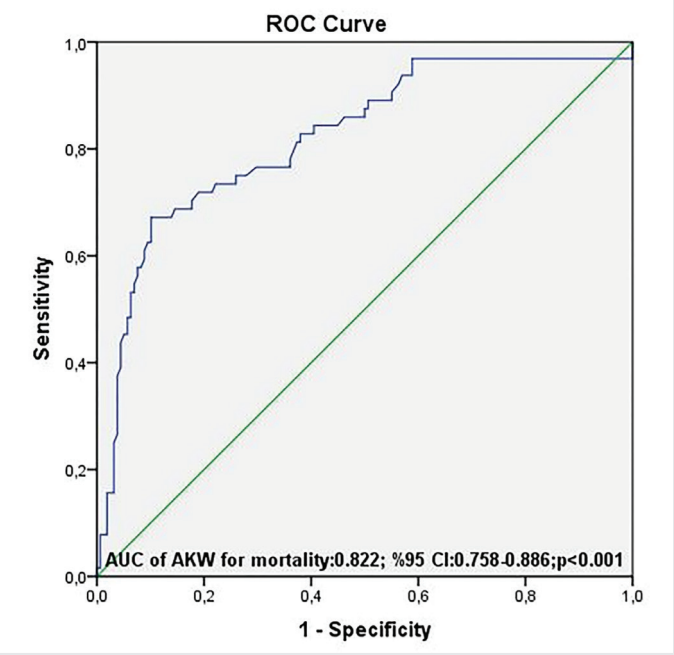

Figure 1. ROC curve of AKW to predict in-hospital mortality in patients with COVID-19
AKW: Aortic knob width, ROC: Receiver operating characteristic, CI: Confidence interval, AUC: Area under the curve, COVID-19: Coronavirus disease-2019

organ failure, circulatory shock, metabolic problems, and in some cases, death (18,19). Studies have suggested numerous parameters that can predict the prognosis in these patients.

In a local study by Burhamah et al. (20) in Kuwait, parameters that could affect the prognosis were investigated in 133 patients who were admitted to intensive care due to COVID. As a result of the study, mechanical ventilation during admission to the hospital, development of in-hospital complications, presence of kidney failure, leucocytosis, LDH, and urea levels were found to be closely associated with in-hospital mortality. In another study conducted by Nasrullah et al. (21) on 58 patients in Pennsylvania; they found the in-hospital mortality rate to be 32.8% and investigated the factors associated with mortality. The analysis demonstrated that multiple variables were markedly linked to an increased likelihood of death. These included advanced age, elevated Charlson comorbidity score, rapid breathing, low lymphocyte count at admission, higher APACHE ratings, circulatory collapse, onset of ARDS, need for ventilatory support, and corticosteroid administration.

Moreover, a new oxygen requirement at discharge was observed in 44.7% of individuals who could be discharged from the intensive care unit, and this was also important in terms of showing the severity of the disease. In another local study, the relationship of hematological parameters and comorbidities with COVID-19 severity in patients hospitalized for COVID-19 was investigated. In this study involving 306 participants, patients were categorized as either severe or non-severe COVID-19 cases. The findings indicated that CRP, D-dimer, and ferritin levels at the time of hospital admission were significantly associated with disease severity (22). Chauhan et al. (23) conducted a study involving 125 hospitalized COVID-19 patients, exploring how admission-time demographic characteristics and laboratory findings were associated with patient outcomes. They found that advanced age, presence of ischemic heart disease, smoking history, as well as high D-dimer and LDH levels at admission, and low lymphocyte counts were associated with mortality.

Inflammation plays an important role in COVID-19 infection. In their study of 720 COVID-19 patients who presented to the emergency department and were found to have PCR positivity, Toori et al. (24) concluded that neutrophil-lymphocyte ratios measured at the time of admission were associated with mortality as well as the severity of the disease. They suggested that the neutrophil to lymphocyte ratio has the important advantage of being inexpensive and easily available 24/7. In a study conducted in China, researchers showed that high NLR and LDH levels are closely related to the severity and course of the disease, and especially combining these two parameters will increase the sensitivity of the diagnosis (25). In a separate study involving 695 patients, Asan et al. (26) examined the link between hematologic markers and both disease severity and prognosis in COVID-19. They found that NLR, PLR, and LYM × PLT values measured at admission were significantly associated with disease severity and held predictive value for patient outcomes. Similarly, in our study, we found that NLR levels as well as SII, were associated with AKW levels, which are associated with prognosis.

In a study similar to ours, Luchian et al. (27) reported that a coronary artery calcium score of zero observed in 280 COVID-19 patients who underwent chest CT might be linked to an increased risk of major adverse cardiovascular events. They concluded that a calcium score of 0 in these individuals had a negative predictive value of 84.5%.

In our study, we investigated the relationship between AKW and mortality in COVID-19 patients, which is a non-invasive method that can be easily calculated and is inexpensive. As a result of our study, the width of the aortic knob, which is closely related to atherosclerosis and is known to be associated with end-organ damage in studies, may be associated with mortality in hospitalized COVID-19 patients. We concluded that in these patients, AKW greater than 40 mm can predict mortality, and AKW values correlate with hematological and laboratory parameters known to affect prognosis. We found a correlation between patients' ages, lengths of hospital stays, d-dimer, NLR, SII, procalcitonin, ferritin, CRP levels, and AKW values.

Study Limitations

First, our study is a cross-sectional single-center study, and patients suitable for hospitalization during a specific period were included. For this reason, local factors must be considered before generalizing our results to wider populations. The treatments applied to hospitalized patients may differ between countries. Additionally, the measurement of AKW may be subject to observer dependence, and inter-observer variability was not assessed in this study. The treatments of the patients in our study were applied in line with the guidelines of the Ministry of Health. During the period when the research records were obtained, vaccination was not yet widespread in our country. Therefore, the number of vaccinated cases in both patient groups was very low and was similar between the groups. For this reason, it is necessary to evaluate the results of the study independently of vaccination procedures.

Conclusion

The chest X-ray obtained at the time of hospital admission in almost all COVID-19 patients, which guides the diagnosis and treatment, is inexpensive, easily applicable, and accessible. It contains valuable information that may be related to their prognosis. AKW measurements appear to correlate with factors that are potentially predictive of mortality in individuals diagnosed with COVID-19. In these individuals, AKW measurement should be made at the time of admission, and individuals with values higher than 40 mm should be followed more carefully throughout the hospitalization process.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 46, date: 11.02.2022).

Informed Consent: An informed consent form was signed by the patients participating in the study, and the relatives of the individuals who were not in a position to give consent.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 293-9
DOI: 10.4274/imj.galenos.2025.05860

Evaluation of the Relationship Between Laboratory Parameters, Severity of Coronary Artery Disease, and Adverse Clinical Outcomes in Patients Undergoing Coronary Angiography

Evliya Akdeniz, Cennet Yıldız

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Türkiye

ABSTRACT

Introduction: Acute coronary syndrome (ACS) continues to represent a major challenge in cardiovascular field despite significant progress in diagnostic and therapeutic interventions. The blood urea nitrogen-to-albumin ratio (BAR), a composite marker easily derived from routine laboratory tests, has recently emerged as a promising indicator in patients with various clinical settings. We aimed to assess the relationship between the BAR and the occurrence of in-hospital major adverse cardiovascular events (MACE) in patients with ACS.

Methods: A retrospective analysis was conducted on patients with ACS between December 2022 and June 2025. Patients were categorized into two groups in terms of in-hospital MACE, defined as all-cause mortality, myocardial infarction (MI), or stroke. Clinical variables associated with MACE were analyzed among the comparative groups. To determine independent predictors of in-hospital MACE, both univariate and multivariate logistic regression analyses were conducted. Furthermore, the discriminatory ability of the BAR for predicting in-hospital MACE was evaluated through receiver operating characteristic (ROC) curve analysis.

Results: Eight hundred twenty nine patients were included in the study, and 61 (7.4%) experienced in-hospital MACE. Patients who experienced in-hospital MACE had a significantly elevated BAR values compared to those who did not (2.33 vs. 1.58; $p<0.001$). Multivariate logistic regression analysis revealed that BAR was an independent predictor of in-hospital MACE (odds ratio: 1.312; 95% confidence interval: 1.010-1.703; $p=0.042$), alongside ST-elevation MI, SYNTAX (SYNergy between PCI with TAXUS™ and Cardiac Surgery) score and lower levels of hemoglobin and serum albumin. ROC curve analysis demonstrated that BAR had a good ability to discriminate between patients who did and did not experience in-hospital MACE, with an area under the curve of 0.784. A BAR cut-off value of 1.72 was identified, offering a sensitivity of 85.2% and a specificity of 61.2% for predicting in-hospital MACE.

Conclusion: Our findings suggest that the BAR, a simple, cost-effective biomarker routinely available in clinical practice, is independently associated with in-hospital MACE in ACS patients.

Keywords: Acute coronary syndrome, BUN to albumin raito, BAR, ACS, MACE

Introduction

Despite significant advances in diagnostic methods, medical therapy, and interventional cardiology, ischemic heart disease continues to be the foremost contributor to mortality globally (1). Acute coronary syndromes (ACS) constitute a principal cause of mortality and morbidity within the spectrum of cardiovascular diseases (2). The spectrum of ACS includes unstable angina pectoris (UAP) and non-ST-elevation myocardial infarction (NSTEMI), collectively referred to as non-ST elevation ACS, as well as ST-elevation myocardial infarction (STEMI). Although the in-hospital mortality of clinical entities within the ACS spectrum has led to a decline over recent years, according to data from the Global Registry of Acute Coronary Events (GRACE), the overall in-hospital mortality rate for patients with ACS remains significant, reported at 3.6% (3,4).

The inflammatory mechanism has a central role in the process of vascular atherogenesis and the development and prognosis of ACS. Clinical studies demonstrating the beneficial effects of anti-inflammatory therapies on clinical outcomes further support this relationship (5-7). Numerous laboratory parameters have been recognized as markers of systemic inflammation, among which hypoalbuminemia has been identified as a particularly significant and clinically pertinent biomarker

Address for Correspondence: Evliya Akdeniz MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Cardiology, İstanbul, Türkiye
E-mail: evliyakdeniz@gmail.com **ORCID ID:** orcid.org/0000-0002-4688-7992

Cite this article as: Akdeniz E, Yıldız C. Evaluation of the relationship between laboratory parameters, severity of coronary artery disease, and adverse clinical outcomes in patients undergoing coronary angiography. İstanbul Med J. 2025; 26(4): 293-9

Received: 03.08.2025
Accepted: 01.10.2025
Publication Date: 12.11.2025

of inflammation (8,9). Beyond inflammation, renal function holds significant importance in patients with ACS, both in terms of guiding treatment strategies and influencing prognosis. Impaired renal function has been consistently recognized as a significant determinant of poor clinical outcomes, including mortality and myocardial infarction (MI), in patients with ACS (10,11).

Renal function constitutes a critical determinant in both the therapeutic approach and prognostic evaluation of patients with ACS. Decline in renal function has been consistently linked to increased mortality among ACS patients, underscoring its prognostic significance in this population (12,13). Blood urea nitrogen (BUN) is a metabolic waste product generated during the catabolism of proteins within the body. It is predominantly eliminated via renal excretion, indicating that BUN levels may be a critical biomarker for evaluating renal function. While it is commonly used as an indirect marker of kidney function, BUN levels can also be affected by other conditions such as increased protein breakdown, dehydration, or gastrointestinal bleeding, making it a reflection of both renal and systemic health (14,15).

In light of the established clinical relevance of both albumin and BUN levels, the blood urea nitrogen-to-albumin ratio (BAR) has emerged as a composite biomarker, with studies demonstrating its significant association with adverse clinical outcomes across various patient populations (16,17).

The management of ACS necessitates a comprehensive and multifaceted approach, which involves rapid clinical evaluation, incorporation of biomarker data, interpretation of electrocardiographic findings, and the utilization of advanced imaging techniques, as well as timely revascularization procedures, when clinically indicated. Building on this clinical framework, we aimed to investigate the potential relationship between the BAR and the incidence of in-hospital major adverse cardiovascular events (MACE), including death, MI, and stroke, among patients presenting with ACS. Through this analysis, our objective was to enhance understanding of the prognostic significance of BAR within this high-risk cohort, during the vulnerable hospitalization period, thereby contributing to improved risk stratification and potentially guiding more personalized therapeutic decision-making.

Methods

Study Population

This retrospective study analyzed data from patients hospitalized with a confirmed diagnosis of ACS between December 2022 and June 2025. The selected timeframe facilitated the systematic collection and analysis of clinical and demographic data, thereby enabling a rigorous evaluation of patient outcomes and contributing factors within a well-defined hospital cohort. All participants underwent coronary angiography and/or percutaneous coronary intervention as part of the management of ACS. SYNTAX (SYNergy between PCI with TAXUS™ and Cardiac Surgery) score was used to determine the anatomical burden and distribution of coronary atherosclerotic involvement (18). The inclusion criteria were age older than 18 years and admission with a confirmed diagnosis of ACS, encompassing STEMI, NSTEMI, or UAP. Laboratory data were evaluated based on blood samples collected at the time of admission. To ensure an accurate assessment of the BAR, only patients with documented measurements of both BUN and serum albumin upon admission were deemed eligible for inclusion in the study. Exclusion criteria were as follows: subjects with dialysis-dependent end-stage kidney disease; advanced hepatic dysfunction; active malignancy undergoing treatment; a known chronic inflammatory or infectious disease that could interfere with the interpretation of inflammatory biomarkers; incomplete medical records; missing laboratory data, including BUN or serum albumin levels; those who underwent coronary artery bypass graft surgery during hospitalization; active gastrointestinal bleeding; corticosteroid use; and refusal to participate in the study.

Baseline demographic characteristics, along with pertinent clinical and laboratory parameters, were systematically retrieved from the hospital's electronic medical records. The study cohort was stratified into two groups according to the occurrence of in-hospital MACE: MACE (+) group and the control group. Clinical variables associated with MACE were analyzed between the comparative groups, and independent predictors of MACE development were identified.

The study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2022-12-05, date: 09.07.2025). This study was carefully conducted with full respect for the ethical principles outlined in the Declaration of Helsinki, underscoring our deep commitment to research integrity and the well-being of all participants.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Comparisons between patients with and without in-hospital MACE were conducted using the independent Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Comparative analysis of categorical variables was performed using the chi-square test. A receiver operating characteristic (ROC) curve was constructed to evaluate the predictive value of the BAR for in-hospital MACE. Univariable logistic regression analysis was used to identify potential predictors of in-hospital MACE, and variables that reached statistical significance in the univariable analysis were subsequently included in a multivariable logistic regression model to determine independent predictors. Due to the strong correlation between BUN and creatinine levels, only BUN was included in the multivariable analysis. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA).

Endpoint

The primary endpoint of our study was in-hospital MACE, which included death, MI, and stroke.

Results

The study encompassed a total of 829 individuals who met the inclusion criteria and were subsequently enrolled, of whom 61 (7.4%) experienced MACE. Among these, death occurred in 39 patients (4.7%), MI in 15

patients (1.81%), and stroke in 7 patients (0.84%). While the MACE group was slightly older (61.05±10.92 vs. 59.31±11.17 years), the difference in age was not statistically significant between groups (p=0.241). Two groups were comparable across several baseline characteristics, including sex, smoking status, diabetes mellitus, hypertension, and cerebrovascular accident history. However, STEMI rates were higher in the MACE group (75.4% vs. 56%, p=0.013), which was also characterized by a higher mean SYNTAX score. Laboratory findings showed that patients in the MACE group had significantly lower serum albumin and hemoglobin levels, as well as reduced left ventricular ejection fraction (LVEF) compared to those in control group. In contrast, patients in the MACE group exhibited higher neutrophil counts, admission glucose, BUN, creatinine, and troponin levels compared to the control group. The BAR was found to be markedly higher in the group that experienced MACE when compared to the control group with values of 2.33 and 1.58, respectively (p<0.001). Baseline characteristics, laboratory, and clinical variables are presented in Table 1.

A univariate logistic regression analysis was conducted to systematically evaluate potential variables linked to the occurrence of in-hospital MACE. STEMI exhibited a notable linkage to MACE [odds ratio (OR): 2.411, 95% confidence interval (CI): 1.323-4.392, p=0.004], 2.411, 95%CI: 1.323-4.392, p=0.004). Hemoglobin, serum albumin levels, and LVEF demonstrated an inverse relation with in-hospital MACE, while SYNTAX score, neutrophil counts, serum glucose, BUN, creatinine, and troponin levels were positively related with an increased risk of MACE. Notably, the BAR demonstrated a strong relation to MACE (OR: 1.552, 95% CI: 1.273-1.892, p<0.001), highlighting its potential as a composite prognostic indicator in terms of in-hospital MACE. Table 2 summarizes the findings of the univariate analysis.

To comprehensively evaluate the factors independently associated with MACE, a multivariate logistic regression analysis was performed. STEMI presentation, SYNTAX score, and declined hemoglobin in conjunction with suppressed serum albumin levels was found to be significant predictors of MACE. BAR was significantly associated with MACE (OR: 1.312, 95% CI: 1.010-1.703, p=0.042), suggesting that an increase in BAR is independently linked to a higher likelihood of experiencing major adverse cardiovascular outcomes (Table 3).

These statistical findings suggest that BAR remained independently associated with in-hospital MACE, even after adjusting for well-established prognostic indicators such as STEMI presentation, SYNTAX score, hemoglobin concentration, and serum albumin levels. This

Table 1. Comparison of baseline clinical and laboratory characteristics between patients with and without major adverse cardiovascular events

Variable	Overall (n=829)	Control group (n=768)	MACE group (n=61)	p
Age (years)	59.44±11.15	59.31±11.17	61.05±10.92	0.241
Female (%)	184 (22.2)	170 (22.1)	14 (23)	0.883
Smoker (%)	404 (48.7)	381 (49.6)	23 (37.7)	0.073
DM (%)	304 (36.7)	279 (36.3)	25 (41)	0.468
HTN (%)	451 (54.4)	420 (54.7)	31 (50.8)	0.559
CVA (%)	40 (4.6)	35 (4.6)	5 (8.2)	0.207
Type of ACS				0.013
STEMI (%)	476 (57.4)	430 (56)	46 (75.4)	
NSTEMI (%)	252 (30.4)	241 (31.4)	11 (18)	
UAP (%)	101 (12.2)	97 (12.6)	4 (6.6)	
SYNTAX score	15.5 (9.00-22.50)	15.00 (9.00-22.00)	19.00 (13.25-33.00)	0.001
Hemoglobin (g/dL)	13.90 (12.70-15.90)	14.00 (12.80-15.10)	13.00 (12.65-15.30)	0.001
Platelet (10^9/L)	237 (201-285)	238 (200.75-285)	235 (199.5-284)	0.792
Neutrophils (10^9/L)	6.07 (4.39-8.70)	6.00 (4.30-8.55)	7.30 (5.35-10.22)	0.009
Lymphocytes (10^9/L)	2.12 (1.56-2.89)	2.12 (1.59-2.87)	1.87 (1.29-3.14)	0.294
LDL (mg/dL)	113.50 (84.00-141.00)	114.00 (84.00-141.00)	106.50 (81.75-138.50)	0.594
Glucose (mg/dL)	129.5 (104.00-185.25)	127.00 (103.00-175.65)	172.00 (130.00-263.00)	<0.001
BUN (mg/dL)	69.76 (55.64-87.74)	68.90 (54.83-85.60)	83.24 (66.98-109.78)	<0.001
Creatinine (mg/dL)	0.90 (0.76-1.07)	0.90 (0.76-1.06)	1.01 (0.78-1.33)	0.014
Albumin (g/L)	42.80 (40.00-45.50)	43.00 (40.60-45.60)	36.30 (35.00-37.60)	<0.001
BAR (BUN/Albumin Ratio)	1.61 (1.28-2.07)	1.58 (1.26-2.00)	2.33 (1.81-3.14)	<0.001
Troponin (ng/L)	58.00 (12.00-410.00)	49.23 (11.00-372.00)	191.00 (38.00-980.00)	<0.001
LVEF (%)	55.00 (45.00-60.00)	55.00 (45.00-60.00)	47.50 (35.00-55.00)	0.001

ACS: Acute coronary syndrome, BAR: BUN-to-albumin ratio, BUN: Blood urea nitrogen, CVA: Cerebrovascular accident, DM: Diabetes mellitus, HTN: Hypertension, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, MACE: Major adverse cardiovascular events, NSTEMI: Non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, SYNTAX: SYNergy between PCI with TAXUS™ and Cardiac Surgery, UAP: Unstable angina pectoris

underscores its potential as a valuable adjunctive tool in the early risk stratification process. BAR may capture additional dimensions of patient vulnerability.

ROC curve analysis was conducted to assess the ability of the BAR to predict the occurrence of MACE. BAR is a valuable predictor of MACE with an area under the curve of 0.784 (95% CI: 0.735-0.883, p<0.001) and demonstrates good overall discriminative performance. A discriminatory threshold of 1.72 was identified, providing a sensitivity of 85.2% and a specificity of 61.2% (Figure 1).

Table 2. Univariate logistic regression analysis of variables associate with major adverse cardiovascular events

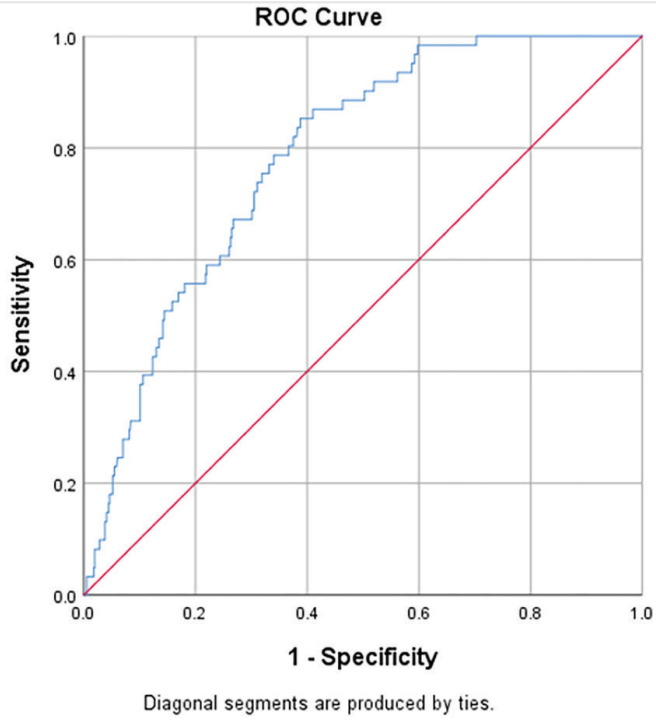
Variable	Odds ratio	95% confidence interval	p
STEMI	2.411	1.323-4.392	0.004
SYNTAX score	1.061	1.031-1.093	<0.001
Hemoglobin	0.803	0.702-0.918	0.001
Neutrophil	1.100	1.037-1.166	0.001
Glucose	1.005	1.003-1.007	<0.001
BUN	1.007	1.003-1.012	0.001
Creatinine	1.002	1.001-1.086	0.043
Albumin	0.842	0.799-0.887	<0.001
BAR	1.552	1.273-1.892	<0.001
Troponin	1.002	1.001-1.003	0.016
LVEF	0.961	0.937-0.985	0.002

BAR: Blood urea nitrogen to albumin ratio, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, STEMI: ST segment elevation myocardial infarction, SYNTAX: SYNergy between PCI with TAXUS™ and Cardiac Surgery

Table 3. Multivariate logistic regression analysis of independent predictors for major adverse cardiovascular events

Variable	Odds ratio	95% confidence interval	p
MODEL A			
STEMI	4.189	1.430-12.273	0.009
SYNTAX score	1.042	1.000-1.086	0.043
Hemoglobin	0.799	0.637-0.997	0.049
Neutrophil	1.031	0.907-1.172	0.643
Glucose	1.002	0.997-1.007	0.464
BUN	1.004	0.996-1.011	0.342
Albumin	0.778	0.709-0.854	<0.001
Troponin	1.000	0.999-1.000	0.148
LVEF	1.003	0.953-1.055	0.914
MODEL B			
STEMI	4.641	1.682-12.809	0.003
SYNTAX score	1.037	1.002-1.077	0.046
Hemoglobin	0.760	0.618-0.935	0.009
Neutrophil	1.049	0.935-1.176	0.417
Glucose	1.001	0.997-1.006	0.539
Troponin	1.000	0.999-1.000	0.289
LVEF	1.005	0.960-1.052	0.823
BAR	1.312	1.010-1.703	0.042

BAR: Blood urea nitrogen to albumin ratio, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, STEMI: ST segment elevation myocardial infarction, SYNTAX: SYNergy between PCI with TAXUS™ and Cardiac Surgery



	AUC	p-value	95% CI	Cutoff	Sensitivity (%)	Specificity (%)
BAR	0.784	<0.001	0.735 – 0.883	1.72	85.2	61.2

Figure 1. Receiver operating characteristic curve analysis of BAR for predicting in-hospital MACE
AUC: Area under curve, BAR: Blood urea nitrogen to albumin ratio, CI: Confidence interval, ROC: Receiver operating characteristic, MACE: Major adverse cardiovascular events

Discussion

In our study, we examined the relationship between the BAR and the incidence of in-hospital MACE, including death, MI, and stroke, among patients with ACS. Through this investigation, our objective was to examine the role of BAR as a readily accessible and cost-effective biomarker designed to enable prompt risk assessment in individuals with ACS, a population inherently at increased risk. Several noteworthy findings emerged from our analysis, highlighting the potential of BAR as an independent predictor of in-hospital adverse cardiovascular outcomes. The main goal of the present study is not only to clarify the prognostic significance of BAR in this high-risk cohort but also to contribute to the expanding body of evidence that supports the integration of easily obtainable biomarkers into clinical risk assessment frameworks during hospitalization.

Among the key findings, one of the most was that BAR emerged as an independent predictor of in-hospital MACE. This finding indicates that an elevated BAR value is associated with a significantly increased risk of in-hospital MACE, with an OR of 1.312, suggesting that patients with higher BAR levels have a notably greater likelihood of MACE during hospitalization. In addition to BAR, STEMI presentation, lower hemoglobin, and decreased serum albumin levels were also identified as independent predictors of MACE.

BUN, a byproduct of protein catabolism, serves not only as a routine biochemical marker but also as a clinically significant prognostic indicator across a range of medical conditions. Its serum concentration reflects the interplay between hepatic urea production and renal excretory function, and is modulated by various physiological and pathological factors, including dietary protein intake, volume status, and renal function (14,15,19-21). Seki et al. (14) reported that elevated BUN levels were independently associated with unfavorable renal outcomes, suggesting BUN may hold prognostic value in anticipating the progression of kidney disease. Additionally, there is compelling scientific evidence demonstrating that renal function plays a critical role in the clinical course and outcomes of patients with ACS. Renal dysfunction is well established as a critical factor influencing the prognosis of patients with ACS. An expanding body of evidence underscores the critical impact of impaired kidney function on patient outcomes, revealing that individuals with compromised renal function face a significantly higher risk of in-hospital mortality, along with an increased likelihood of long-term mortality. This association persists across diverse patient populations and clinical settings, highlighting the importance of early identification and comprehensive management of kidney dysfunction as an integral component of improving both immediate and long-term prognoses (11,13). In our study, the primary endpoint was MACE. Importantly, renal function has been shown to be associated not only

with mortality but also with other key components of MACE, including MI and stroke. Evidence indicates that impaired kidney function serves an independent risk factor for both MI and stroke (22,23).

Serum albumin, a key plasma protein, plays an essential role in maintaining oncotic pressure and serves as a marker of nutritional and inflammatory status (24,25). Serum albumin levels participate significantly in determining the prognosis of cardiovascular diseases. In patients with ACS, low serum albumin levels are associated with both in-hospital and long-term mortality (26,27). In addition to its association with mortality, hypoalbuminemia may play an etiological role in the development of stroke. In a study conducted by Zhang et al. (28), a significant association was identified between low serum albumin levels and the risk of recurrent ischemic stroke. Moreover, inflammation plays a pivotal role in the molecular mechanisms underlying both coronary artery disease and ACS, serving as one of the key drivers in disease initiation and progression (7,25). Low serum albumin levels have been consistently associated with systemic inflammation and are considered a reliable marker of both nutritional and inflammatory status (29).

The BAR has emerged as a novel and accessible biomarker that reflects multiple critical physiological domains, including volume status, renal function, protein metabolism, nutritional status, and systemic inflammation. Elevated BUN levels often reflect underlying renal dysfunction, volume depletion, or heightened catabolic processes, whereas reduced serum albumin concentrations commonly signify systemic inflammation, compromised nutritional status, and poorer clinical prognosis. The integration of these two biomarkers into the BAR offers a more holistic evaluation of a patient's physiological state, capturing both metabolic and inflammatory dimensions that might be overlooked when considering each parameter independently.

When considered alongside the aforementioned scientific evidence, the findings of our study indicate that the BAR offers clinicians a valuable and practical biomarker for predicting the risk of in-hospital MACE in patients presenting with ACS. As a clinical index derived from routinely obtained laboratory parameters, the BAR offers a practical, accessible, and cost-effective tool for daily clinical use. Its ease of application and ability to reflect underlying physiological disturbances make it particularly valuable for predicting adverse clinical outcomes, thus supporting timely and informed decision-making in patient care.

The integrative nature of the BAR facilitates a more comprehensive evaluation of a patient's underlying physiological status, surpassing the insights provided by isolated laboratory parameters. This multidimensional approach enables clinicians to discern complex pathophysiological interactions that contribute to adverse cardiovascular outcomes, which may otherwise remain undetected. The robust and independent predictive capability of BAR for in-hospital MACE in patients with ACS underscores its potential utility as a critical instrument for early risk stratification. Such timely identification of high-risk individuals is essential for optimizing clinical decision-making processes and judicious allocation of healthcare resources. Furthermore, the derivation of BAR from routine laboratory tests confers substantial advantages in terms of accessibility, cost-effectiveness, and feasibility, particularly within diverse clinical environments including those constrained by limited resources or time pressures. These pragmatic attributes facilitate prompt risk assessment and enable the implementation of more intensive monitoring and personalized therapeutic strategies tailored to patient-specific needs. In this regard, BAR complements established risk scoring systems and clinical evaluations, enriching the clinician's ability to adopt a holistic and individualized approach to patient management. Ultimately, this integrative biomarker serves not only to enhance prognostic precision but also to support improved clinical outcomes and promote more efficient utilization of healthcare resources.

Study Limitations

This study is subject to several limitations that merit careful consideration. First, its retrospective nature and single-center design may constrain the generalizability of the findings to broader, more heterogeneous patient populations across diverse healthcare settings. Such limitations underscore the need for caution when extrapolating these results beyond the studied cohort. Second, the assessment of albumin and BUN levels was confined to a single measurement upon admission. The absence of serial biomarker evaluations during hospitalization precludes a comprehensive understanding of temporal fluctuations and their potential prognostic implications. Longitudinal monitoring of these parameters could yield critical insights into their dynamic relationship with disease progression and clinical outcomes. Third, the predictive value of the BAR for long-term clinical outcomes could not be evaluated due to the absence of follow-up data beyond the in-hospital period. A notable limitation of our study is the restricted use of multivariable models. The absence of adjustments for other well-established risk predictors in ACS, such as Killip class and components of the GRACE score, limits the strength of our conclusions regarding the independent predictive value of the BAR.

Conclusion

Our study sheds light on the emerging relevance of the BAR as a meaningful and practical biomarker of adverse clinical outcomes in the care of patients with ACS. What makes BAR particularly compelling is its ability to reflect multiple aspects of a patient's physiological state-encompassing kidney function, nutritional status, and systemic inflammation-all of which are known to influence clinical outcomes but are often assessed in isolation. By combining these factors into a single, cost-effective, reproducible, and easy-to-calculate ratio, BAR offers clinicians a more complete picture of patient risk at the time of admission. Its routine availability and low cost make it especially useful in real-world settings where time and resources may be limited. Still, while our findings are promising, they represent a step rather than a destination. Larger, prospective studies across varied patient groups will be essential to confirm BAR's role and determine how best it can complement current risk assessment tools. Ultimately, integrating such accessible biomarkers into everyday practice could help clinicians make more informed, timely, and personalized decisions-improving care during the most critical phases of treatment.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2025-12-05, date: 09.07.2025).

Informed Consent: Retrospective study.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 300-6
DOI: 10.4274/imj.galenos.2025.29498

Evaluation of the Relationship Between Five Different Insulin Resistance Indices and Glycemic Control in Patients with Prediabetes and Type 2 Diabetes

Sinem Aydın, Levent Deniz, Özlem Demirelce

University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Medical Biochemistry, İstanbul, Türkiye

ABSTRACT

Introduction: This study was designed for comparing the performance of insulin resistance (IR) indices in individuals with prediabetes and type 2 diabetes mellitus (T2DM).

Methods: Participants were classified into four categories according to HbA1c using the American Diabetes Association criteria: control group (<5.7%) (n=192), prediabetes (5.7%-6.4%) (n=147), regulated T2DM (6.5%-7.0%) (n=28), and non-regulated T2DM (>7.0%) (n=61). Patient records and laboratory information system data were reviewed to determine serum glucose, triglyceride, high-density lipoprotein cholesterol (HDL-C), insulin, and to determine homeostatic model assessment of IR (HOMA-IR), insulin sensitivity index (ISI/McAuley index), quantitative insulin sensitivity check index (QUICKI), triglyceride to HDL-C ratio (TG/HDL-C), and triglyceride-glucose (TyG) index.

Results: The non-regulated T2DM group had higher HOMA-IR and TyG levels and lower QUICKI values than the prediabetic and regulated T2DM groups. TyG and HOMA-IR indices have a positive correlation with HbA1c (r=0.547 and r=0.456, respectively). According to the receiver operating characteristic analysis, TyG had the highest area under the curve (AUC) of 0.749 (0.705-0.789) to identify patients with HbA1c ≥5.70%, and the Turkish population-specific cut-off value was set at 8.55. Findings from the binary logistic regression highlighted that TyG, HOMA-IR, TG/HDL-C, QUICKI, and ISI indices were associated with patients with HbA1c ≥5.70%, independent of age and sex.

Conclusion: Among the evaluated IR indices, the TyG index demonstrated the highest correlation coefficient with HbA1c. In addition, it yielded the largest AUC, indicating superior diagnostic performance compared to the other indices. These findings suggest that the TyG index may serve as a useful marker of IR in individuals with prediabetes and T2DM.

Keywords: HbA1c, type 2 diabetes mellitus, TyG index, QUICKI, HOMA-IR

Introduction

A rising health concern, type 2 diabetes mellitus (T2DM) increases the risk of macrovascular and microvascular complications due to hyperglycemia and insulin resistance (IR) (1). The prognosis of patients with T2DM is largely determined by the level of disease control; chronic hyperglycemia is associated with a higher risk of microvascular complications, as evidenced by studies (2). Therefore, achieving effective glycemic control and improving insulin sensitivity are crucial for minimizing the likelihood of T2DM-associated complications. Recognizing the individuals who are at an elevated risk of DM and determining the course of the disease are key strategies for preventing and managing diabetes.

Over the last few decades, many different methods have been used to measure IR and determine glycemic control. The hyperinsulinemic-euglycemic clamp is commonly used as the gold standard method for assessing IR, although it is complicated and requires specialized expertise (3). The most commonly used method of measurement is the homeostatic model assessment of IR (HOMA-IR), which is an easier, although less accurate, method (4). It requires fasting insulin levels, which is relatively expensive and not available in many laboratories. Therefore, an easy-to-use, reliable, and affordable index for evaluating glycemic control and IR is crucial. Recently, several novel and readily accessible tools have been developed to predict IR.

This study aimed to evaluate and compare the performance of IR indices, including HOMA-IR, triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), triglyceride-glucose (TyG) index, insulin sensitivity index (ISI/McAuley index), and quantitative insulin

Address for Correspondence: Sinem Aydın MD, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Medical Biochemistry, İstanbul, Türkiye
E-mail: sinem00aydin@gmail.com **ORCID ID:** orcid.org/0009-0007-2945-4945

Cite this article as: Aydın S, Deniz L, Demirelce Ö. Evaluation of the relationship between five different insulin resistance indices and glycemic control in patients with prediabetes and type 2 diabetes. İstanbul Med J. 2025; 26(4): 300-6

Received: 16.04.2025
Accepted: 01.10.2025
Publication Date: 12.11.2025

sensitivity check index (QUICKI), in predicting patients diagnosed with prediabetes and T2DM.

Methods

Ethics approval for this study was approved by the University of Health Sciences Türkiye, İstanbul Traning and Research Hospital, Clinical Research Ethics Committee (approval number: 16, date: 25.01.2025). All stages of this study were designed in accordance with the rules of the Declaration of Helsinki. Medical records of 428 patients who attended the Family Medicine outpatient clinic at University of Health Sciences Türkiye, İstanbul Training and Research Hospital between January and December 2018 were retrospectively reviewed. We included participants aged 18-65 years who were tested for HbA1c, fasting glucose, fasting insulin, fasting TG, and HDL-C levels by reviewing their patient folders and laboratory information system records. Patients with type 1 diabetes mellitus, those who are pregnant, have cardiovascular diseases, malignancy, hematological disorders, liver or kidney diseases, or autoimmune disorders were excluded from this study.

We categorized patients with HbA1c concentrations higher than 5.7% into three groups: prediabetic (5.7%-6.4%) (n=147), regulated T2DM (6.5%-7.0%) (n=28), and non-regulated T2DM (>7.0%) (n=61), using criteria set by the American Diabetes Association (5,6). Patients with HbA1c levels below 5.7% were taken as the control group (n=192).

Laboratory Parameters

All measurements were performed using venous blood samples after an overnight fast of at least 8 hours. Fasting glucose, total cholesterol (TC), HDL-C, and TG levels were analyzed using the analytical chemistry system AU5800 (Beckman Coulter Inc., Brea, California, US). Insulin levels were quantified via the DxI800 (Beckman Coulter Inc., Brea, California, US). Measurement of HbA1c was performed with the ADAMS A1c HA8180V (Arkray, Kyoto, Japan). HOMA-IR values were derived by the following formula: fasting insulin (mU/L) × fasting glucose (mg/dL) / 405 (7). TyG index calculated as ln [fasting Triglyceride (mg/dL) x fasting glucose (mg/dL)/2] (8). Triglyceride/HDL-C was calculated as TG (mg/dL)/ HDL-C (mg/dL). QUICKI figured out as 1/[log(fasting insulin, mIU/L) + log(fasting glucose, mg/dL)] (9). ISI (McAuley Index) calculated as e(2.63-0.28*lnFI-0.31*lnTG) (TG refers to triglyceride levels in mmol/L and FI refers to fasting insulin levels in mIU/L) (10).

Statistical Analysis

The Shapiro-Wilk test was conducted to evaluate the distribution of the data. Continuous data are presented as mean ± standard deviation or median (25^{th} and 75^{th} percentiles), and discrete data as numbers (percentages). Discrete data were analyzed using the Pearson chi-square test. Comparative studies among the groups were conducted by employing one-way ANOVA and the Kruskal-Wallis analysis according to the distribution characteristics of the data. Bonferroni-adjusted p-values were used to control for type 1 errors in multiple pairwise comparisons (n=6), with the threshold for statistical significance set at p<0.008. The association between each index and both HbA1c and HOMA-IR was evaluated using Spearman correlation analysis. To assess the discriminative power of the indices in identifying individuals with elevated HbA1c levels (≥5.70%), receiver operating characteristic (ROC) analysis was applied. Binary logistic regression was conducted, both univariate, and multivariate, for patients with HbA1c levels higher than 5.70%. Considering the multicollinearity among the IR indices, separate logistic regression analyses were performed for each index to assess their individual predictive relationships with the outcome variable. Statistical evaluation and graphical representation were applied using SPSS 26 (IBM C.A., US) and GraphPad Prism v. 8.3.0 (GraphPad Software, US). Although a general threshold value of p<0.05 was applied for statistical significance, a criterion of p<0.008 was employed for multiple pairwise comparisons (n=6) due to the Bonferroni correction.

Results

Of all the groups included in the study, 165 (38.6%) were men and 263 (61.4%) were women. The mean age of the patients was 50±11 years. There was no difference in age between the prediabetic, regulated T2DM, and non-regulated T2DM groups. The non-regulated T2DM group had a higher proportion of males than the prediabetic and control groups. Age, glucose, insulin, TC, TG, HOMA-IR, TyG, and TG/HDL-C were higher in the prediabetic group than in the control group. QUICKI and ISI were lower in the prediabetic population than in the controls. Age, glucose, TG, TyG, HOMA-IR, and TG/HDL-C were higher in the regulated T2DM group than in the control group, whereas QUICKI and ISI indices were lower in the regulated T2DM group than in the control group. Age, glucose, insulin, TG, TyG, HOMA-IR, and TG/HDL-C levels were higher in the non-regulated T2DM group than in the controls, whereas QUICKI and ISI indices were lower in the non-regulated T2DM group than in controls. Glucose levels and TyG index were higher in the regulated T2DM group than in the prediabetic group. Glucose, TyG, HOMA-IR, and TG/HDL-C levels were higher in the non-regulated T2DM group than in the prediabetic group, whereas HDL-C, QUICKI were lower in the non-regulated T2DM group than in the prediabetic group. TyG and HOMA-IR levels were higher in the non-regulated T2DM group than in the regulated T2DM group, whereas the QUICKI was lower in the non-regulated T2DM group than in the regulated T2DM group (Table 1 and Figure 1).

TyG level (r=0.547, p<0.001), TG/HDL-C (r=0.306, p<0.001), and HOMA-IR (r=0.456, p<0.001) have positive correlations with HbA1c level. QUICKI (r=-0.457, p<0.001) and ISI (r=-0.345, p<0.001) had a negative correlation with HbA1c levels. The correlation coefficient between TyG and HbA1c was higher than those between other indices. HOMA-IR levels were positively correlated with TyG (r=0.559, p<0.001) and TG/HDL-C ratio (r=0.485, p<0.001). Conversely, QUICKI (r=-1.000, p<0.001) and ISI (r=-0.821, p<0.001) were negatively correlated with HOMA-IR (Table 2 and Figure 2).

Among the indices assessed through ROC analysis for identifying individuals with HbA1c ≥5.70%, TyG had the largest area under the curve (AUC) of 0.749 [95% confidence interval (CI) =0.705-0.789]. The AUC value for HOMA-IR was 0.727 (95% CI =0.682-0.769). QUICKI had an AUC level of 0.724 (95% CI =0.679-0.766). The ISI had an AUC of 0.675 (95% CI =0.629-0.720). TG/HDL-C ratio had an AUC of 0.635 (95% CI =0.587-0.681) (Table 3 and Figure 3).

Table 1. Comparison of demographic characteristics and laboratory findings between the groups

Parameter	Control (n=192)	Pre-diabetic (n=147)	Regulated T2DM (n=28)	Non-regulated T2DM (n=61)	p*
Age (years)	46.0 (35.0-55.0)	57.0 (50.3-62.0) a^2	55.5 (51.0-59.5) a^2	57.0 (52.8-61.0) a^2	**<0.001**
Gender n (%) Female Male	 120 (62.5%) 72 (37.5%)	 104 (70.7%) 43 (29.3%)	 14 (50.0%) 14 (50.0%)	 25 (40.9%) 36 (59.1%)	**<0.001**
Glucose (mg/dL)	89.5 (84.0-95.5)	101 (94.3-109)a^2	119 (108-127) a^2, b^1	178 (136-227)a^2, b^2	**<0.001**
Insulin (mU/L)	6.69 (4.64-10.1)	8.61 (5.98-13.0) a^2	8.19 (5.94-11.9)	10.4 (6.29-16.3) a^2	**<0.001**
TC (mg/dL)	212 (175-240)	227 (193-258) a^1	228 (186-282)	220 (187-260)	**0.012**
TG (mg/dL)	103 (72.5-155)	129 (95.3-191) a^2	165 (129-194) a^2	157 (107-233) a^2	**<0.001**
HDL-C (mg/dL)	49.0 (40.0-60.0)	51.0 (43.0-58.8)	49.0 (40.0-57.0)	45.0 (39.0-53.3) b^1	**0.044**
LDL-C (mg/dL)	138 (108-161)	145 (121-173)	147 (111-185)	134 (109-159)	0.077
TyG index	8.48±0.54	8.84±0.53 a^2	9.12±0.36 a^2, b^1	9.63±0.77 a^2, b^2, c^2	**<0.001**
HOMA-IR	1.49 (1.01-2.38)	2.16 (1.47-3.31) a^2	2.68 (1.80-3.46) a^2	4.75 (3.05-7.07) a^2, b^2, c^1	**<0.001**
QUICKI	0.36 (0.34-0.38)	0.34 (0.32-0.36) a^2	0.33 (0.32-0.35) a^2	0.30 (0.29-0.32) a^2, b^2, c^1	**<0.001**
TG/HDL-C	2.17 (1.27-3.47)	2.65 (1.77-4.04) a^1	3.18 (2.51-4.34) a^1	3.58 (2.20-6.13) a^2, b^1	**<0.001**
ISI	7.62 (6.28-9.33)	6.64 (5.61-7.83) a^2	6.34 (5.67-7.11) a^2	5.89 (4.92-7.40) a^2	**<0.001**

*p<0.05, considered statistically significant. Bonferroni correction was used for pairwise comparisons of the four groups, with significance set at p<0.008. a^1: p<0.008, a^2: p<0.001, a: Comparison with controls, b^1: p<0.008, b^2: p<0.001, b: Comparison with prediabetics, c^1: p<0.008, c^2: p<0.001, c: Comparison with regulated type 2 DM group
DM: Diabetes mellitus, TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index, T2DM: Type 2 diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol

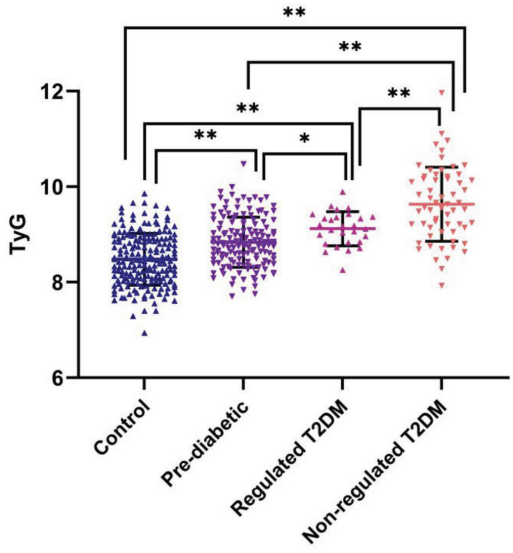

Figure 1. Comparison of the TyG index among the control, prediabetic, regulated T2DM, and non-regulated T2DM groups.
*p<0.008, **p<0.001, TyG: Triglyceride glucose, T2DM: Type 2 diabetes mellitus

In the univariate logistic regression analysis applied to identify patients with HbA1c levels higher than 5.70%, TyG, HOMA-IR, and TG/HDL-C indices showed positive predictive values, whereas QUICKI and ISI indices demonstrated negative predictive values. Independent of age and sex, TyG, HOMA-IR, TG/HDL-C, QUICKI, and ISI indices were significantly associated with HbA1c levels higher than 5.70% (Table 4).

Discussion

IR is an essential trigger in the development of microvascular and macrovascular complications. In addition according to the diabetes complications and control trial study (11), glycemic control with HbA1c maintained under 7.0% significantly decreased the likelihood of microvascular and macrovascular complications. We aimed to identify the most specific, sensitive, and inexpensive biochemical predictor of IR in prediabetic and diabetic patients. Therefore, IR indices were investigated as potential indicators in patients with prediabetes and diabetes, who were divided into three categories based on HbA1c values. Ethnicity, socioeconomic characteristics, and dietary patterns of the population have been shown to cause differences in IR. Few studies have suggested cut-offs for TyG, TG/HDL-C, QUICKI, and ISI values in Turkish prediabetic and diabetic adult populations. The study by Aslan Çin et al. (12) on TyG and TG/HDL-C indices was conducted in an obese adolescent cohort, and found TG/HDL-C >2.16, TyG >8.50, and HOMA-IR >2.52. Dundar et al. (13) determined separate cut-offs for TyG in obese girls and boys. In adults, Kırtıl et al. (14) found the value for the TyG index in individuals with impaired glucose tolerance to be 4.44 using the [FG (mg/dL) × fTG (mg/dL)]/2 formula. For QUICKI, Gokcel et al. (15) study on the Turkish adult hospital population also found a value of 0.347±0.028. Fakı et al. (16) revealed that the TyG index is associated with diabetic nephropathy in patients with T2DM.

Although elevated TG and reduced HDL-C levels, when considered separately, are commonly detected in individuals with T2DM and IR, they are weaker risk indicators than TG/HDL-C. Performance of TG/HDL-C has been outlined as being almost the same as those for fasting insulin concentration in determining IR in overweight individuals (17). In a cohort study by Liu et al. (18), as in our study, an increased TG/HDL-C level was reported to be a significant indicator for T2DM risk, independent of gender and age. Similar to our findings, numerous earlier research have identified a positive relationship between TG/HDL-C and the occurrence of T2DM (19-21). According to Chauhan et al. (22), high TG/HDL-C levels may contribute to the early detection of

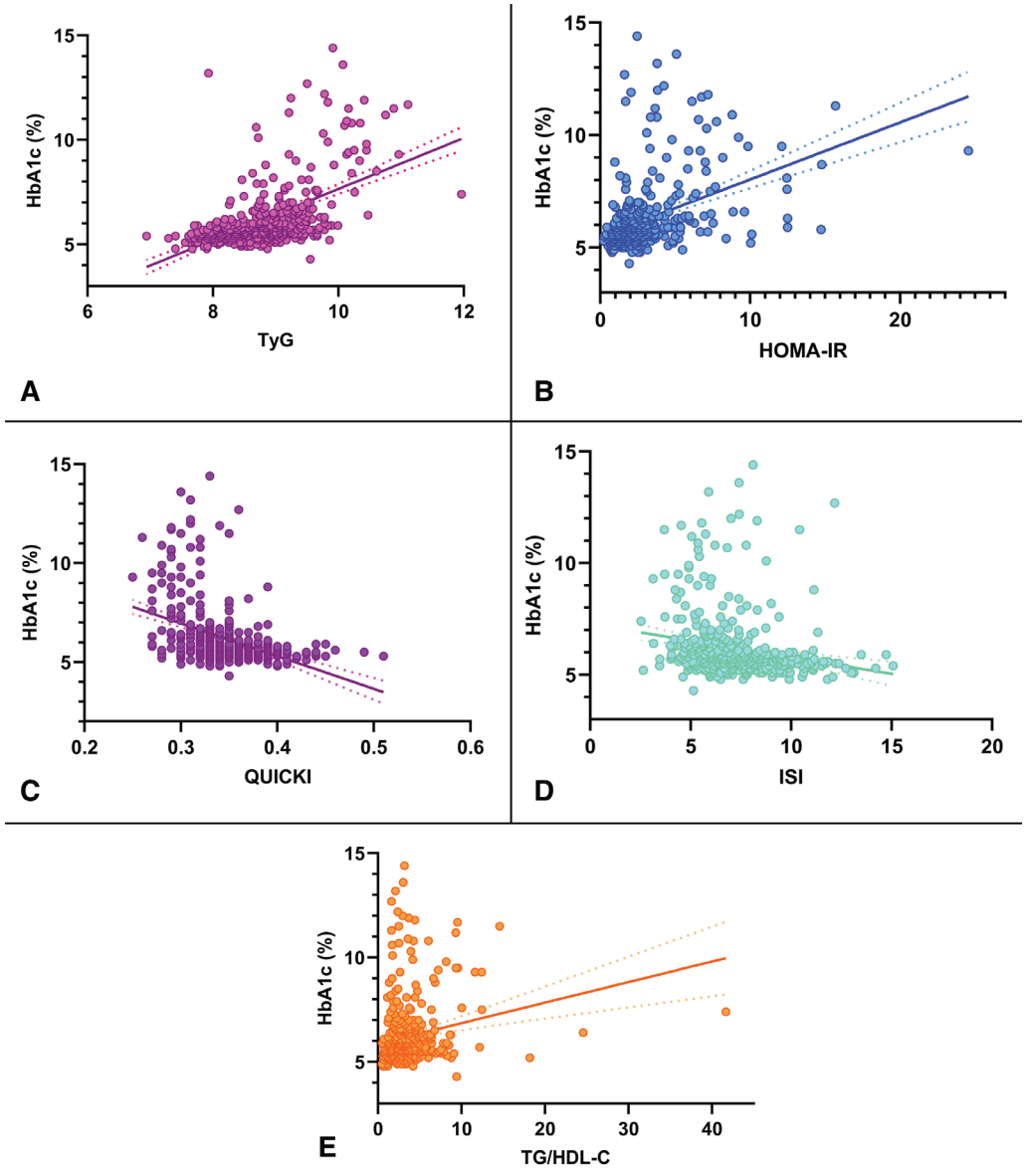

Figure 2. Correlations between HbA1c and (a) TyG, (b) HOMA-IR, (c) QUICKI, (d) ISI, and (e) TG/HDL-C ratio in all groups
TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index

Table 2. Correlations between indices and HbA1c (%) and HOMA-IR in all groups

Parameter	HbA1c (%)		HOMA-IR	
	r	p	r	p
TyG index	0.547	<0.001	0.559	<0.001
HOMA-IR	0.456	<0.001	1.000	<0.001
QUICKI	-0.457	<0.001	-1.000	<0.001
ISI	-0.345	<0.001	-0.821	<0.001
TG/HDL-C	0.306	<0.001	0.485	<0.001

TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index

atherosclerotic complications, even in prediabetes. In support of this, we found a significant difference (p<0.008) in TG/HDL-C values between the prediabetic and control groups. Chen et al. (23) highlighted the association between higher baseline TG/HDL-C or TyG levels and an elevated risk of T2DM in prediabetic individuals. Similar to our findings, TyG showed superior predictive power for the risk of DM.

Several studies have reported that TyG is related to the risk of DM and may be a valuable biomarker (24-27). In our study, we found that among the indices investigated, TyG best demonstrated the development and progression of diabetes in the Turkish adult population [AUC=0.749, (95% CI =0.705-0.789), with 79.7% sensitivity and 57.3% specificity]. When we examined the development of diabetes using the correlations of the indices with HbA1c and HOMA-IR, we found that TyG was their best indicator (r=0.547, p<0.001; r=0.559, p<0.001, respectively). Navarro-González et al. (27) suggested a TyG index cutoff value of 8.8 for incident IR and T2DM. In our study, we determined the cut-off level for the TyG index to be 8.55 in the prediabetic and diabetic groups. Additionally, Lee et al. (25) identified a TyG index cut-off level of 8.86 in men and 8.52 in women for predicting T2DM in middle-aged Koreans. Our cut-off value may be slightly lower because of the inclusion of the prediabetes group in the evaluation, and ethnic differences. This value is predictive for future studies conducted in larger populations in our country.

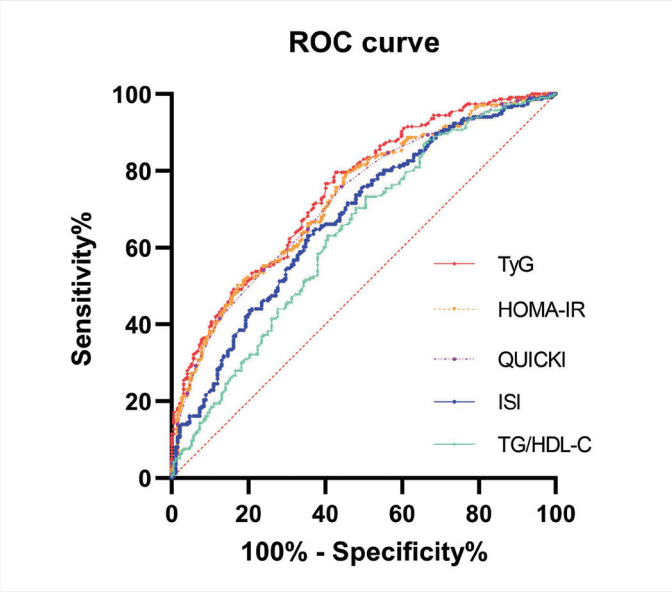

Figure 3. Receiver operating curve analysis of IR indices in determining individuals with HbA1c levels ≥5.7%
TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index, ROC: Receiver operating characteristic

Katz et al. (28) defined QUICKI as potentially useful in clinical research. In an investigation by Yokoyama et al. (29), QUICKI was highly correlated with Clamp-IR in T2DM patients with relatively wide fasting plasma glucose ranges. In a study conducted by Sarafidis et al. (30), QUICKI was confirmed as a valid tool for assessing T2DM patients; however, they stated that further studies should be conducted for McAuley's index. According to a study by Straczkowski et al. (31), in individuals with normal glucose tolerance, fasting insulin levels in plasma may be sufficient as a crude indicator of insulin sensitivity because beta cell function is intact. However, in cases of prediabetes and diabetes, indices based on logarithmically transformed data, such as QUICKI and plasma glucose levels, are recommended. In our study, we found an important difference between the prediabetic, diabetic, and control groups for both tests (Table 1), and significant negative correlations between QUICKI-HbA1c, QUICKI-HOMA-IR, McAuley index-HbA1c and McAuley index-HOMA-IR in all groups (Table 2).

Table 3. Receiver operating curve analysis of the indices for patients with HbA1c levels higher than 5.70%

Index	AUC	95% CI	Cut-off	Sensitivity	Specificity	p
TyG Index	0.749	0.705-0.789	>8.55	79.7%	57.3%	<0.001
HOMA-IR	0.727	0.682-0.769	>1.56	79.7%	54.2%	<0.001
QUICKI	0.724	0.679-0.766	≤0.35	75.9%	55.7%	<0.001
ISI	0.675	0.629-0.720	≤6.98	63.1%	64.6%	<0.001
TG/HDL-C	0.635	0.587-0.681	>2.06	73.3%	49.5%	<0.001

TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index, AUC: Area under the curve, CI: Confidence interval

Table 4. Binary logistic regression analysis for patients with HbA1c levels higher than 5.70%

Parameter	Unadjusted		Adjusted*	
	OR (95% CI)	p	OR (95% CI)	p
TyG	5.40 (3.61-8.09)	**<0.001**	4.12 (2.65-6.41)	**<0.001**
HOMA-IR	1.62 (1.39-1.89)	**<0.001**	1.65 (1.39-1.95)	**<0.001**
QUICKI	0.00 (0.00-0.00)	**<0.001**	0.00 (0.00-0.00)	**<0.001**
ISI	0.73 (0.66-0.81)	**<0.001**	0.76 (0.68-0.85)	**<0.001**
TG/HDL-C	1.19 (1.08-1.31)	**<0.001**	1.12 (1.01-1.23)	**0.029**

*Adjusted for age and sex. Dependent variable: control (HbA1c <5.70%) vs. patient groups (HbA1c ≥5.70%)
TyG: Triglyceride glucose, HOMA-IR: Homeostatic model assessment for insulin resistance, QUICKI: Quantitative insulin sensitivity check index, TG/HDL-C: Triglyceride-to-high-density lipoprotein cholesterol, ISI: Insulin sensitivity index, CI: Confidence Interval, OR: Odds ratio

A study has shown that an elevated TyG index and HOMA-IR in T2DM patients are associated with a higher risk of diabetic kidney disease (DKD). Using HOMA-IR in combination with the TyG index provided higher sensitivity and specificity in predicting DKD than HOMA-IR alone (32). The correlation between the TyG index and albuminuria in T2DM patients was found to be higher than the correlations with other IR indices, such as HOMA-IR, visceral adiposity index, and lipid accumulation product (33). In some studies, an independent association between the TyG index and diabetic retinopathy was identified in patients with T2DM, even after controlling for confounding variables (34,35). Among patients with T2DM, those diagnosed with cardiac autonomic neuropathy (CAN) exhibited significantly elevated TyG index and elevated HbA1c levels, in comparison to their counterparts without CAN (36,37). In patients with T2DM, the TG/HDL-C ratio demonstrated the highest AUC (0.721) for predicting coronary artery disease, whereas TyG-waist circumference exhibited the highest specificity (78%) (38). In another study, ROC analyses showed that metabolic score for IR had a higher AUC and better predictive power than the TyG index in defining major adverse cardiovascular events (39). IR indices may play an important role in identifying and managing the risk of complications in patients with T2DM. Their use may enhance early detection, risk stratification, and personalized intervention, ultimately improving patient outcomes.

Study Limitations

Because our study was cross-sectional and had a relatively small sample size, a study with more data points is necessary to clarify cause-and-effect relationships. In addition, instead of the hyperinsulinemic euglycemic clamp, HOMA-IR was used to determine IR in this study. Finally, some factors, such as body mass index, possible comorbidities, diet, characteristics of standard of living, and the use of statins or other drugs, could not be included in the study.

Conclusion

Among the evaluated IR indices, the TyG index demonstrated the highest correlation coefficient with HbA1c. In addition, it yielded the largest AUC, indicating superior diagnostic performance to the other indices. These findings indicate that the TyG index may serve as a useful indicator of IR in individuals with prediabetes and T2DM.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, İstanbul Traning and Research Hospital, Clinical Research Ethics Committee (approval number: 16, date: 25.01.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Concept - S.A.; Design - S.A., L.D.; Data Collection or Processing - S.A., L.D., Ö.D.; Analysis or Interpretation - S.A., L.D., Ö.D.; Literature Search - S.A., L.D., Ö.D.; Writing - S.A., L.D., Ö.D.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 307-12
DOI: 10.4274/imj.galenos.2025.71780

Diagnostic Accuracy of Albumin Levels in Predicting Colistin-Induced Nephrotoxicity in Critically ill Patients in the Intensive Care Unit

Yakup Özgüngör, Şeyma Baykan, Mensure Yılmaz Çakırgöz
University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital, Clinic of Anesthesiology Critical Care, İzmir, Türkiye

ABSTRACT

Introduction: Colistin is an antibiotic utilized for the treatment of drug-resistant bacterial infections. Despite its efficacy, colistin is associated with significant nephrotoxicity, reported in up to 40% of cases. Hypoalbuminemia has been identified as a potential risk factor for acute kidney injury (AKI), but its predictive role in colistin-induced nephrotoxicity remains unclear. This study examines the relationship between hypoalbuminemia and the occurrence of AKI in critically ill patients undergoing colistin treatment.

Methods: This retrospective cohort study was conducted in a tertiary intensive care unit between 2020 and 2022. Patients aged 18 years or older who received colistin for at least 48 hours were included, excluding those with chronic kidney disease, high-dose vasopressor use, or advanced liver failure. Data on demographics, clinical characteristics, and laboratory findings were collected. AKI was diagnosed using KDIGO criteria, and hypoalbuminemia was defined as albumin <2.5 g/dL. Statistical analyses, including logistic regression, were performed using SPSS 26.0, with significance set at $p<0.05$.

Results: Among 104 patients, 49 (47.1%) developed AKI. Patients with AKI were older (mean age 66.7 vs. 59.1 years, $p=0.016$) and had longer durations of hypoalbuminemia (median 18 vs. 6 days, $p<0.001$). Hypoalbuminemia at the start of colistin therapy was significantly associated with AKI ($p<0.001$). Logistic regression identified low albumin levels as an independent predictor of AKI (odds ratio 0.14, $p=0.005$). Mortality was higher in the AKI group (57% vs. 43%, $p=0.003$).

Conclusion: Hypoalbuminemia is a significant predictor of colistin-induced AKI. Early identification and management of hypoalbuminemia may reduce nephrotoxicity and improve outcomes in critically ill patients receiving colistin therapy. Further multicenter studies are recommended to validate these findings.

Keywords: Hypoalbuminemia, colistin, nephrotoxicity

Introduction

Colistin, or polymyxin E, is an antibiotic first discovered in Japan in 1949 and produced by *Paenibacillus polymyxa*, a gram-positive bacterium. It disrupts gram-negative bacterial membranes by binding to lipid A in lipopolysaccharides and displacing calcium and magnesium ions, increasing membrane permeability and causing cell death. Among the five polymyxins (A-E), only polymyxin B and colistin are used clinically. Initially introduced for human and veterinary use in 1952, colistin was largely replaced by less toxic alternatives, but resurged as a last-resort treatment against multidrug-resistant gram-negative bacteria. The European Medicines Agency classifies colistin as a category B ("Restrict") antibiotic, recommended only when other treatments are ineffective (1).

Human albumin (albumin) is the principal protein in the blood of healthy individuals, with a concentration range of 3.5-5 g/dL. In healthy individuals, the liver synthesizes approximately 10-15 grams of albumin per day. The plasma half-life of albumin ranges from 12 to 19 days. Albumin plays a crucial role in maintaining plasma oncotic pressure, accounting for approximately 70-80% of the total oncotic pressure, thereby regulating fluid exchange between body compartments. This oncotic pressure is influenced by both the osmotic effect of the molecule's mass and its negative charge, which attracts sodium and, consequently, water (2).

The most notorious and feared side effect of colistin therapy is nephrotoxicity, which is reported in the literature, at rates approaching 40%.3 The exact mechanism underlying colistin-induced nephrotoxicity remains incompletely understood, but it is believed to involve direct proximal tubular cell damage and oxidative stress, ultimately leading to AKI. Various risk factors have been proposed to predict and prevent AKI during colistin therapy. Among patient-related risk factors, male sex, advanced age, obesity, diabetes mellitus, impaired liver function tests, and hyperbilirubinemia have been identified as contributors to increased susceptibility. Additionally, treatment-related factors such as septic

Address for Correspondence: Yakup Özgüngör MD, University of Health Sciences Türkiye, İzmir Tepecik Traning and Research Hospital, Clinic of Anesthesiology Critical Care, İzmir, Türkiye
E-mail: jacobozgungor@gmail.com **ORCID ID:** orcid.org/0000-0002-1370-1696

Cite this article as: Özgüngör Y, Baykan Ş, Yılmaz Çakırgöz M. Diagnostic accuracy of albumin levels in predicting colistin-induced nephrotoxicity in critically ill patients in the intensive care unit. İstanbul Med J. 2025; 26(4): 307-12

Received: 24.01.2025
Accepted: 02.10.2025
Publication Date: 12.11.2025

shock, prolonged therapy duration, high-dose colistin administration, concurrent use of nephrotoxic agents, and multiple antibiotics or drugs use further elevate the risk (3,4). Additionally, hypoalbuminemia has been associated with deterioration in renal function (4,5).

Consequently, efforts have been made both to explore protective measures against nephrotoxicity and to develop new antibiotics (6). Although newly developed antibiotics like the combination of ceftazidime-avibactam are considered safer in terms of nephrotoxicity, their use in developing countries like ours is subject to stringent criteria (7). Therefore, colistin treatment remains a vital option (8). The aim of the study is to determine whether albumin levels and the duration of hypoalbuminemia can be used to predict colistin-induced nephrotoxicity.

Methods

This retrospective cohort study was conducted in a tertiary intensive care unit (ICU) between 2020 and 2022. Patients aged 18 years or older who received colistin therapy for at least 48 hours were included. Inclusion criteria were a baseline glomerular filtration rate (GFR) of ≥60 mL/min/1.73m² to ensure normal renal function before colistin initiation, AKI within the 48 hours prior to colistin therapy, and no history of chronic kidney disease (CKD) or prior renal replacement therapy (RRT). Exclusion criteria were as follows: pre-existing CKD with a baseline GFR below 60 mL/min/1.73 m², high-dose vasopressor use (greater than 0.25 mcg/kg/min norepinephrine or equivalent), advanced liver failure (Child-Pugh C), and patients already receiving RRT at baseline. The study was reviewed by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital (approval no: 2011-KAEK-25 2023/02-09, date: 08.03.2023).

Demographic characteristics, clinical data, and laboratory values were retrieved from electronic medical records. Data included age, sex, comorbidities (diabetes, hypertension, cardiovascular disease, COPD), infection site (pulmonary, urinary, bloodstream), and mortality. Laboratory parameters included albumin levels, urea, creatinine, and inflammatory markers. GFR was calculated at baseline; however, it was not recalculated at the stage of AKI development due to the inability to obtain a stable creatinine level, which would result in inaccurate estimations (9).

Patients who developed AKI were identified based on their baseline creatinine levels, following the KDIGO recommendations. Accordingly, AKI was defined as an increase in serum creatinine of ≥0.3 mg/dL within 48 hours or an elevation to ≥1.5 times the baseline within the same period. The severity of AKI was determined based on the KDIGO staging system (9).

Hypoalbuminemia was defined as a serum albumin level <2.5 g/dL. The duration of hypoalbuminemia was calculated as the number of days the patient's albumin level remained below this threshold before the initiation of colistin therapy.

Antibiotics administered concomitantly with colistin were recorded. Patients who received a known nephrotoxic antibiotic (e.g., vancomycin) simultaneously with colistin initiation were excluded from the study. However, if such antibiotics had been administered at least 48 hours before colistin initiation, then their use was documented, and these patients were included in the study. Similarly, patients who had received nephrotoxic drugs such as angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, contrast agents, or calcineurin inhibitors within the last 48 hours were excluded from the study. However, those with a history of use of these drugs beyond this timeframe were included.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Normally distributed data were reported as means with standard deviations and compared using the independent samples t-test. Non-normally distributed data were expressed as medians with interquartile ranges (IQR) and analyzed using the Mann-Whitney U-test. Categorical variables were presented as frequencies and percentages, and differences between groups were assessed using the chi-square test or Fisher's exact test. A binary logistic regression was performed to identify predictors of AKI, with AKI as the dependent variable (binary AKI present or absent). Independent variables included age, albumin levels at the start of colistin treatment, and the duration of hypoalbuminemia. Odds ratios (OR) with 95% confidence intervals were reported, with a p-value <0.05 considered statistically significant.

Results

As per the study, by AKI stages, 55 patients (52.9%) did not develop AKI, 7 patients (6.7%) were in stage 1 AKI, 19 patients (18.3%) were in stage 2 AKI, and 23 patients (22.1%) were in stage 3 AKI.

Patients who developed AKI were significantly older, with a mean age of 66.73±14.722 years, compared to patients who did not develop AKI, with a mean age of 59.09±16.798 years; p=0.016. There was no significant difference in the severity scores regarding SAPS, APACHE-II, and GKS, with p-values of 0.679, 0.424, and 0.194, respectively.

The albumin levels at admission, based on laboratory values, were not significantly different between the two groups (p=0.51). However, the AKI group had significant hypoalbuminemia at the start of therapy, 2.1 (IQR 2.000-2.400) g/dL compared to the non-AKI group of patients at 2 (1.680-2.200) g/dL, with a p-value of <0.001. The duration of hypoalbuminemia was longer in patients with AKI development compared to those without (median 18 days vs. 6 days, p<0.001). Among those who developed AKI, 37 (75.5%) did not receive RRT, 10 (20.4%) received continuous veno-venous hemodiafiltration (CVVHDF), and 2 (4.1%) received intermittent hemodialysis (IHD). After the discontinuation of colistin, 43 (87.7%) of the patients did not require RRT; 5 (10.2%) continued to require CVVHDF; and 1 (2.1%) was treated with IHD. During the treatment, 29 (27.9%) patients died. At the three-month follow-up, among all the patients, only 1 (1.0%) patient received IHD because of permanent kidney damage; 53 (51%) died, and 50 (48%) recovered sufficiently, not to require RRT. On the 14th day post-treatment, 35 (71.4%) of the patients who developed AKI recovered fully. Creatinine levels remained up to twice the baseline in 4 (6.5%) patients, between two to three times the

baseline in 7 (11.3%) patients, and more than three times the baseline in 6 (9.7%) patients. Table 1 provides a comparison of demographic characteristics, comorbidities, and infection sites.

Figure 1 shows the albumin level at the time of antibiotic initiation and the duration of hypoalbuminemia (in days) following the initiation of antibiotics. The best cut-off point for the duration of hypoalbuminemia, as determined by the receiver operating characteristic (ROC) curve analysis, was found to be 9.50 days. At this threshold, the sensitivity of the model is 73.5%, and the 1-specificity ratio is 36.4%.

The optimal cut-off value for the initial albumin level at the start of antibiotic treatment, as determined by the ROC curve analysis, was found to be 1.95 g/dL. At this threshold, the sensitivity of the model is 53.1%, and the 1-specificity is 14.5%.

The baseline demographic and clinical characteristics of the study population, including comorbidities and causes of ICU admission, are detailed in Table 1. The distribution of infection sites and isolated microorganisms is presented in Table 2. The distribution of concomitant medications potentially associated with nephrotoxicity between patients with and without AKI is presented in Table 3. Laboratory findings, including serum albumin, urea, creatinine, and inflammatory markers, are summarized in Table 4. As shown in Table 5, logistic regression analysis identified albumin level at the start of treatment as an independent predictor of AKI development.

Table 6 displays the proportion of patients across different AKI stages.

Table 1. Patient characteristics

Characteristics and risk factors	Not developed AKI	Developed AKI	p-value
Patient (%)	55 (52)	49 (48)	
Males n (%)	41 (40)	31 (30)	0.213
Females n (%)	14 (13)	18 (17)	0.213
Age, years, mean ± SD**	59.09±16.798	66.73±14.722	0.015
SAPS, mean ± SD**	42.42±14.004	43.48±14.732	0.679
APACHE-II, median (IQR)*	14 (11.00-25.90)	17 (17.00-31.20)	0.424
GKS, median (IQR)*	13 (0.00-15.00)	10 (0.00-15.00)	0.194
Comorbidity, n (% total case)*** Diabetes mellitus Hypertension Coronary artery disease COPD Cancer Stroke	 18 (17.3) 26 (25.0) 15 (14.5) 8 (7.7) 12 (11.5) 9 (8.7)	 17 (16.3) 25 (24.05) 14 (13.4) 7 (6.7) 11 (10.6) 8 (7.7)	 0.832 0.703 0.866 0.970 0.747 0.996
Cause of admission, n (% total case)*** Infection COVID-19 Other infection Medical Surgery	 37 (35.58) 22 (21.15) 15 (14.42) 4 (3.85) 14 (13.46)	 31 (29.81) 21 (20.19) 10 (9.62) 9 (8.65) 9 (8.65)	 0.668 0.768 0.413 0.088 0.358

p-values were determined using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test or chi-square test for categorical variables
*Non-normal distribution, mean value and the interquartile range (IQR) is provided
**Normal distribution,median value and standard deviation (SD) is provided, Mv: Mechanical ventilation
***Chi-square test was conducted
COPD: Chronic obstructive pulmonary disease, ACEI: Angiotensin-converting enzyme inhibitors, NSAID: Non-steroidal anti-inflammatory drugs, ARB: Angiotensin II receptor blockers, COVID-19: Coronavirus disease-19, AKI: Acute kidney injury. The percentages are calculated based on the total number of patients

Table 2. Infection site and microorganism

Characteristics and risk factors	Not developed AKI	Developed AKI	p-value
Site of infection, n (% total case)***			
Lung***	27 (26.0)	22 (21.2)	0.669
Urinary***	18 (17.3)	15 (14.4)	0.817
Cranial****	0 (0.0)	2 (1.9)	0.220
Bloodstream****	3 (2.9)	5 (4.8)	0.471
Other****	2 (1.9)	0 (0.0)	0.497
Unkown ****	5 (4.8)	5 (4.8)	>0.99
Patogen, n (% total case)			
Negative ****	6 (5.8)	4 (3.8)	0.746
*Acinetobacter baumannii****	30 (28.8)	22 (21.2)	0.326
*Klebsiella pneumonia****	15 (14.4)	22 (21.2)	0.061
*Pseudomonas aeruginosa*****	4 (3.8)	1 (1.0)	0.367

p-values were determined using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test or chi-square test for categorical variables
***Chi-square test was conducted
****Fisher's exact test was used due to the small sample size (n<5)
AKI: Acute kidney injury

Table 3. Drugs

Characteristics and risk factors	Not developed AKI	Developed AKI	p-value
Drugs***	42	49	0.672
ACEI	2 (1.92)	4 (3.85)	NE
Beta-lactam ***	23 (22.2)	22 (21.15)	>0.476
Quinolone	3 (2.88)	3 (2.88)	NE
Vancomycine	4 (3.85)	2 (1.92)	NE
Fosfomycin	4 (3.85)	0 (0.0)	NE
Aminoglycoside	2 (1.92)	0 (0.0)	NE
Amphotericin	1 (0.96)	0 (0.0)	NE
NSAID	0 (0.0)	1 (0.96)	NE
ARB	2 (1.92)	2 (1.92)	NE
Diuretic	3 (2.88)	2 (1.92)	NE
Contrast media	0 (0.0)	1 (0.96)	NE
Statin	2 (1.92)	2 (1.92)	NE
Antidepressant (fluoxetine)	1 (0.96)	1 (0.96)	NE
Immunosuppressant (calcineurin inhibitor)	1 (0.96)	0 (0.0)	NE
Steroid	1 (0.96)	1 (0.96)	NE
Clopidogrel	2 (1.92)	2 (1.92)	NE

p-values were determined using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test or chi-square test for categorical variables. Due to the small sample sizes, the chi-square test was applied generally to all drugs and specifically to the beta-lactam drug group, which had a sufficiently large sample size
***Chi-square test was conducted
NSAID: Non-steroidal anti-inflammatory drugs, ARB: Angiotensin II receptor blockers, ACEI: Angiotensin-converting enzyme inhibitors, AKI: Acute kidney injury, NE: Not evaluated

Table 4. Laboratory results

Characteristics and risk factors	Not developed AKI	Developed AKI	p-value
Admission albümin ± SD**	2.967±0.4941	2.743±0.6602	0.51
Albumin at the start of therapy median (IQR)*	2.1 (2.000-2.400)	2 (1.680-2.200)	<0.001
Hypoalbuminemia duration (days) (IQR)*	6 (1.00-10.00)	18 (6.00-22.70)	<0.001
Urea, median (IQR) (mg/dL)*	50.5 (39.25-50.50)	56 (35.00-85.00)	0.534
Creatinin, mean ± SD (mg/dL)**	0.7433±0.25655	0.8482±0.48588	0.165
GFR (mL/min/1.73 m^2)*	120 (87-120)	96.75 (73.75-120)	0.058
CRP, median (IQR) (mg/dL)*	127.5 (52.10-157.00)	138 (63.60-112.00)	0.062
WBC median (IQR) (10^3/µL*	11150 (7000.00-11150.00)	9700 (6000.00-9700.00)	0.300
LDH, median (IQR) (U/L)*	325.5(265.00-325.00)	358 (265.00-365.00)	0.817
Length of stay, median (IQR), (days)*	41 (85.00-20.1.00)	54 (63.60-142.00)	0.962
Length of stay at ICU, median (IQR), (days)*	34.5 (26-55.75)	34 (25-60)	0.922
Vasopressor n (%)	23 (50)	23 (50)	0.6
MV n (%)	46 (51)	44(49)	0.358
Duration of treatment, median (IQR), (days)*	10 (7-14)	11.5 (7-14)	0.745
ICU death n (%)	44 (48)	47 (52)	0.014
28 day mortality n (%)	31(43)	41 (57)	0.003

The percentages are calculated based on the total number of patients. p-values were determined using independent samples t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and Fisher's exact test or chi-square test for categorical variables. Due to the small sample sizes, the chi-square test was applied generally to all drugs and specifically to the beta-lactam drug group, which was considered to have a sufficiently large sample size
*Non-normal Distribution, mean value and the interquartile range (IQR) is provided
**Normal distribution,median value and standard deviation (SD) is provided
Mv: Mechanical ventilation, AKI: Acute kidney injury, GFR: Glomerular filtration rate, CRP: C-reactive protein, WBC: White blood cell, LDH: Lactate dehydrogenase, ICU: Intensive care unit

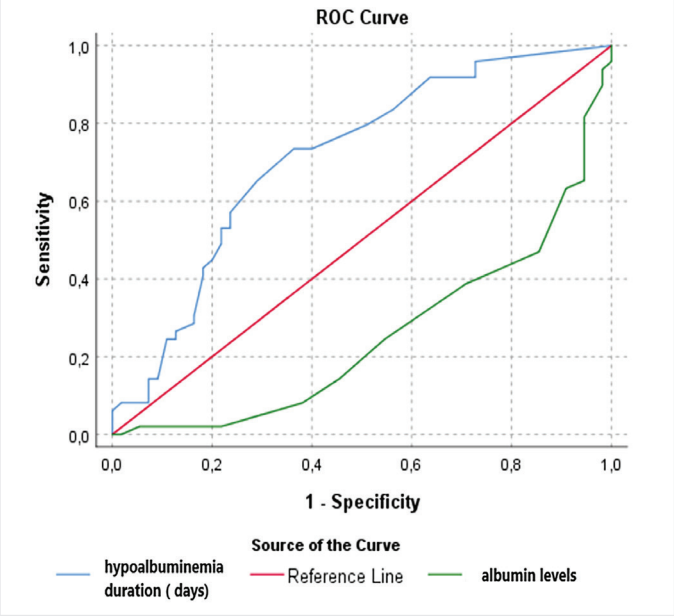

Figure 1. The albumin level at the time of antibiotic initiation and the duration of hypoalbuminemia
ROC: Receiver operating characteristic

Table 5. Binary logistic regression model

Factor	OR (CI 95%)	p-value*
Age	1.018 (0.987-1.050)	0.257
Duration of hypoalbuminemia	1.026 (0.995-1.058)	0.107
Albumin levels at treatment start	0.140 (0.035-0.556)	0.005

*The p-values were calculated using a binary logistic regression model to assess the independent impact of each factor on the development of AKI. Age, duration of hypoalbuminemia, and albumin levels at the start of treatment were included as independent variables in the model
AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval

Table 6. AKI stages

AKI stage n (%) (total AKI patients)	Creatinin mean ± SD (mg/dL)
Stage 1 7 (14.29)	1.500±0.305
Stage 2 19 (38.78)	1.649±0.421
Stage 3 23 (46.94)	2.542±1.39

AKI: Acute kidney injury, SD: Standard deviation

Discussion

In our study, albumin levels were examined as a potential factor influencing colistin-induced nephrotoxicity in critically ill patients receiving colistin therapy in the ICU. Although albumin levels at admission were similar between the AKI and non-AKI groups, the AKI group had significantly lower albumin levels compared to the non-AKI group. The duration of hypoalbuminemia was also evaluated and found to be statistically significant; however, in logistic regression analysis, the duration of hypoalbuminemia did not contribute to the model. Another key finding of our study was that in the majority of patients who developed colistin-induced nephrotoxicity, kidney function returned to normal levels within 14 days after discontinuation of colistin. Among survivors, only one patient developed CKD requiring RRT.

Patients who received nephrotoxic agents such as vancomycin within 48 hours prior to colistin therapy initiation were excluded in order to isolate the nephrotoxic impact of colistin itself. However, patients who had received such agents more than 48 hours prior were included, and

their exposure was recorded. Despite this, due to the small number of patients who had previously received vancomycin (6), we could not perform a subgroup analysis to determine statistically its isolated impact on the development of AKI. Therefore, while we attempted to minimize the confounding effect of concomitant nephrotoxic agents, we acknowledge that prior exposure to such agents may still have contributed to the observed outcomes.

Colistin treatment is associated with nephrotoxicity rates of up to 40% (3). According to our results, AKI developed in 49 patients, accounting for 47.1% of the total study population. This highlights the critical need to identify nephrotoxicity risk factors early and implement preventive strategies to mitigate kidney damage. Several studies have investigated the development of AKI in patients receiving colistin therapy, and various colistin-associated AKI risk factors have been reported (10).

In our study, APACHE II scores did not predict AKI development. While this finding could be interpreted as an indication that there was no significant difference in disease severity and expected mortality between the AKI and non-AKI patient populations, another possible explanation could be incomplete or inaccurate patient records in a retrospective study design. The association between APACHE II scores and AKI prediction has been investigated in the literatüre (11). Moreover, it is important to note that the APACHE II score itself includes serum creatinine levels and the presence of AKI as a parameter.

Vasopressor use was not associated with an increased risk of AKI, as both AKI and non-AKI groups showed similar rates of vasopressor administration (50% in each group, p=0.6). This may be attributed to the exclusion of patients receiving high-dose vasopressors, potentially reducing the nephrotoxic hemodynamic burden. Nevertheless, the absence of an association in our study should be interpreted with caution, considering the relatively small sample size and the inability to analyze vasopressin-specific effects due to lack of dose-specific data.

This study highlights the association between colistin-induced AKI and hypoalbuminemia, demonstrating that lower serum albumin levels significantly increase the risk of nephrotoxicity. The relationship between AKI and hypoalbuminemia has been previously investigated in the literature (12). Colistin exerts nephrotoxic effects through oxidative stress, mitochondrial dysfunction, and direct tubular epithelial damage, particularly in the proximal tubules (6) albumin influences these mechanisms through three primary pathways. First, albumin is essential for maintaining plasma oncotic pressure, thereby supporting renal perfusion. Hypoalbuminemia reduces effective intravascular volume, predisposing patients to renal ischemia and further exacerbating tubular injury (13). In our cohort, this hemodynamic vulnerability likely contributed to the increased AKI rates observed in patients with prolonged hypoalbuminemia. Second, albumin possesses intrinsic antioxidant properties, acting as a buffer against ROS such as peroxynitrite and hypochlorous acid, which are central to colistin-induced tubular injury. Lower albumin levels may impair this protective mechanism, resulting in a more permissive environment for oxidative damage (14). Third, albumin binds to colistin in circulation. A reduction in serum albumin may theoretically increase the free, unbound colistin fraction, thereby amplifying its nephrotoxic potential (15,16). While our study did not measure serum colistin levels, this pharmacokinetic relationship is well supported in the literature. For instance, Sorlí et al. (15) reported that trough plasma levels of colistin correlated independently with nephrotoxicity, suggesting that free colistin is the key driver of renal injury. However, as Nation et al. (17) have pointed out, while hypoalbuminemia may lower total serum colistin concentrations (both bound and unbound), it may not significantly alter the concentration of unbound colistin, which is the toxic fraction responsible for nephrotoxicity. However, since hypoalbuminemia is also an acute-phase reactant, its association with AKI might reflect the overall severity of a patient's condition rather than a direct causal effect. Given this complexity, potential alternative explanations for the heightened risk of AKI in hypoalbuminemic patients should be explored (17). Furthermore, it remains unclear whether targeted albumin replacement in hypoalbuminemic patients can reduce nephrotoxic risk. While albumin supplementation is not routinely recommended for all ICU patients, individualized strategies in the context of high-risk nephrotoxic regimens like colistin may offer a renal-protective benefit worth investigating.

In our study, ROC analysis determined that an albumin level below 1.95 g/dL was the optimal cut-off value for predicting colistin-induced nephrotoxicity. Previous studies have established 3.2 g/dL and 2 g/dL as cut-off values for serum albumin levels (18,19). On the other hand, in a study with 102 colistin-treated patients, hypoalbuminemia was not associated with AKI (15).

To minimize confounding, patients who received nephrotoxic antibiotics concurrently with colistin were excluded, while those treated earlier were included and recorded. Given that colistin is a last-resort antibiotic, most patients receive multiple antimicrobial agents, making colistin monotherapy uncommon.

Furthermore, patients frequently receive nephrotoxic agents for various reasons before colistin initiation. ICU admissions typically involve prolonged hospital stays, making it unlikely for patients to avoid all nephrotoxic exposures before colistin therapy. To address this, a 48-hour exclusion window was established to ensure that patients who had received nephrotoxic agents within this timeframe were excluded. Patients with a history of nephrotoxic agent use prior to this period were included, with their medication history documented. This approach aimed to reduce confounding factors while maintaining the study's generalizability to real-world clinical scenarios.

Study Limitations

The retrospective nature of the design may introduce some bias connected with data collection and analysis. The small sample size might limit the generalization of our findings. Third, the study was carried out at one center and does not represent a broad population. Larger sample sizes and multicenter prospective studies are required to confirm our findings.

Conclusion

Our study highlights the critical role of hypoalbuminemia in colistin-induced nephrotoxicity, demonstrating that lower albumin levels at the initiation of therapy significantly increase the risk of AKI in critically ill patients. ROC analysis identified 1.95 g/dL as the optimal albumin threshold for predicting nephrotoxicity, and logistic regression confirmed albumin levels as an independent predictor of AKI.

Ethics

Ethics Committee Approval: The study was reviewed by the Non-Interventional Research Ethics Committee of University of Health Sciences Türkiye, İzmir Tepecik Training and Research Hospital (approval no: 2011-KAEK-25 2023/02-09, date: 08.03.2023).

Informed Consent: Not required due to the retrospective design of the study.

Footnotes

Authorship Contributions: Concept – Y.Ö.; Design – Y.Ö., M.Y.Ç.; Data Collection or Processing – Y.Ö., Ş.B.; Analysis or Interpretation – Y.Ö., Ş.B.; Literature Search - Y.Ö., M.Y.Ç., Ş.B.; Writing - Y.Ö., M.Y.Ç.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 313-7
DOI: 10.4274/imj.galenos.2025.31384

The Relationship Between Etiology of Wrist Flexor Zone-5 Injuries and Anger Control

Kadir Uzel[1], Erdem Ateş[2], Helin Kan Uzel[3], Zeynel Mert Asfuroğlu[4], Kenan Güvenç[5], Metin Manouchehr Eskandari[4]

[1]İstanbul Medipol University Faculty of Medicine, Department of Orthopaedics and Traumatology and Hand Surgery, İstanbul, Türkiye
[2]Mut State Hospital, Clinic of Orthopedics and Traumatology, Mersin, Türkiye
[3]Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[4]Mersin University Faculty of Medicine, Department of Orthopaedics and Traumatology, Division of Hand Surgery, Mersin, Türkiye
[5]Eskişehir City Hospital, Clinic of Orthopedics and Traumatology and Hand Surgery, Eskişehir, Türkiye

ABSTRACT

Introduction: This study aimed to compare individuals who sustained flexor zone 5 wrist injuries due to punching glass versus accidental work injuries. It focused on anger scales, rehabilitation adherence, and treatment outcomes.

Methods: Forty-eight (9 females, 39 males) cases were reviewed retrospectively. Group A included patients injured by punching glass, while Group B consisted of work-related injuries. Data were collected using Spielberger's Anger scales and a sociodemographic form. Grip strength and QDASH scores were measured at the final follow-up, and the two groups were compared.

Results: Group A had 30 patients (7 females, 23 males), with an average age of 35.43 years (range: 20-56) and a follow-up period averaging 77.73 months (range: 23-135). Group B consisted of 18 patients (2 females, 16 males), with an average age of 46.44 years (range: 25-62) and an average follow-up period of 70.28 months (range: 18-148). Group A, comprising statistically significantly younger males with dominant hand injuries, showed higher uncontrolled anger scores, whereas Group B demonstrated higher anger control scores. There were no significant differences between groups regarding alcohol and/or drug usage, psychiatric history, education, trauma, grip strength, QDASH scores, or rehabilitation compliance.

Conclusion: The majority of injuries from punching glass involved young males with dominant-side injuries and significant anger levels. Although preoperative psychiatric evaluations are not carried out due to the urgent nature of these surgeries, postoperative care should involve hand surgeons, therapists, and psychiatric specialists using a biopsychosocial approach.

Keywords: Hand injury, flexor zone-5, punching glass, anger scales

Introduction

Hand and wrist injuries constitute approximately 15% of all injuries and represent some of the most common traumatic conditions encountered in emergency departments (1-3). Because tendons and neurovascular structures lie in close proximity to the skin and to one another at the wrist level, injuries in this region often involve multiple structures simultaneously (4).

Severe hand and wrist injuries are associated with psychological, social, and economic challenges, as well as long-term disability (5). Such injuries may result from intentional actions, such as punching glass in anger, or from accidental causes, including work, household, recreational, or transportation incidents (6). Approximately 2% of hand injuries caused by glass lacerations are related to punching glass or intentional self-harm (7).

Anger is a universal human emotion; however, when uncontrolled, it can profoundly disrupt an individual's well-being, as well as their social and professional relationships (8). Problems with anger regulation play a critical role not only in the occurrence of such injuries but also in treatment and rehabilitation outcomes. It has been suggested that biopsychosocial factors may influence the results of treatment in cases of intentional self-harm (9).

The aim of this study was to compare patients who sustained flexor zone 5 wrist injuries involving tendons and neurovascular structures caused either by punching glass or by accidental work-related trauma. The comparison focused on anger regulation, adherence to rehabilitation, and treatment outcomes.

Address for Correspondence: Kadir Uzel Asst. Prof., MD, İstanbul Medipol University Faculty of Medicine, Department of Orthopaedics and Traumatology and Hand Surgery, İstanbul, Türkiye
E-mail: dr.k.uzel21@gmail.com **ORCID ID:** orcid.org/0000-0002-3695-9884

Cite this article as: Uzel K, Ateş E, Kan Uzel H, Mert Asfuroğlu Z, Güvenç K, Eskandari MM. The relationship between etiology of wrist flexor zone-5 injuries and anger control. İstanbul Med J. 2025; 26(4): 313-7

Received: 01.07.2025
Accepted: 07.10.2025
Publication Date: 12.11.2025

Methods

Data collection was conducted after obtaining approval from the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (approval number: E-10840098-772.02-5409, date: 01.09.2023). We retrospectively assessed patients who had undergone surgery for three tendon injuries and one nerve injury caused by a flexor zone 5 laceration. Exclusion criteria included patients with follow-up shorter than 18 months, patients who missed more than two of the eight scheduled follow-up visits in the first three months, patients with incomplete data, and patients who declined participation. Ultimately, 48 patients (9 women, 39 men) were included. All participants were adequately informed about the study objectives in accordance with the principles of the Helsinki Declaration, and written informed consent was obtained.

Patients were divided into two groups according to the cause of injury. Group A (n=30) included those injured by punching glass, while Group B (n=18) consisted of patients with unintentional work-related injuries. The mean age was 35.4 years (range, 20–56) in Group A (n=30, 7 women and 23 men) and 46.4 years (range, 25–62) in Group B (n=18, 2 women and 16 men). Injuries to the dominant hand were significantly more frequent in Group A (90%) compared with Group B (11%).

All patients received immediate surgical intervention to identify and repair the damaged structures. The same rehabilitation protocol was applied to all patients after surgery (Table 1).

Patients' anger levels were assessed postoperatively using Spielberger's scales, which include the Trait Anger scale and the Anger Expression Style scale. The Trait Anger scale contains 10 items that measure how frequently individuals experience feelings of anger. The Anger Expression Style scale consists of three subscales: Anger Out, Anger In, and Anger Control, each with 8 items. Responses are scored from 1 (very infrequent) to 4 (very frequent). Higher scores on the Trait Anger scale indicate greater overall anger, higher Anger Out scores reflect a tendency to express anger outwardly, higher Anger In scores suggest anger suppression, and higher Anger Control scores indicate a stronger ability to regulate and manage anger (9-11).

Patients' histories of psychiatric illness, prior trauma, income, education level, marital status, and alcohol or drug use were recorded. Correlation analyses were performed to examine the relationship between Trait Anger and Anger Expression Style scores and variables such as alcohol use, gender, employment status, income, smoking, education, and psychiatric history.

Functional outcomes were evaluated at the last control using grip strength and the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire. Grip strength was measured three times with a Jamar dynamometer, with the elbow flexed at 90 degrees and the forearm and wrist in a neutral position. All measurements were performed by an experienced hand surgeon, and the average of the three values was recorded. QuickDASH scores were calculated from the validated 11-item questionnaire (12).

The two groups were compared based on demographic information, findings during surgery, Trait Anger and Anger Expression Style measures, adherence to the rehabilitation program, and functional outcomes.

Statistical Analysis

The data were analyzed with SPSS software (ver. 29.0; IBM Corp., Armonk, NY, USA). We analyzed the normality of the data using skewness and kurtosis values, which provided the data's symmetry and helped determine its adherence to a normal distribution. We utilized the Pearson chi-squared test and Fisher's exact test for categorical variables, the independent sample t-test for parametric variables, and the Mann Whitney-U test for non-parametric variables. Correlation analyses were performed with Pearson and Spearman tests. Quantitative data were provided as the mean ± standard deviation, and qualitative variables were shown as numbers (n), frequencies, or ratios. A p-value less than 0.05 was considered to have statistical significance.

Results

The analysis revealed significant differences between the two groups in terms of age and dominant-side involvement ($p<0.05$). However, no significant differences were observed between the groups with respect to gender distribution, the number of tendon, nerve, or vessel lacerations, history of alcohol, drug, or cigarette use, history of prior trauma, psychiatric history, marital status, or educational attainment (Table 2).

Table 1. Postoperative rehabilitation protocol

Time/stage	Application
Immobilization	Postoperatively, the wrist was immobilized in a dorsal splint at 15° flexion, with the metacarpophalangeal joints flexed between 40° to 60°, and the interphalangeal joints extended.
Postoperative day 3	Passive finger flexion in the splint was initiated.
First month	Weekly rehabilitation follow-up visits were scheduled. Active flexion was restricted.
End of month 1	The splint was removed and tendon-gliding exercises were initiated.
Month 2 (weeks 5-8)	Biweekly rehabilitation follow-up visits were scheduled.
Week 8	Light resistance training was initiated.
Week 12	Unrestricted activities were permitted.

Although Group A demonstrated higher mean scores for the Trait Anger, Anger Out, and Anger In subscales and Group B showed higher scores for Anger Control, these differences were not statistically significant ($p>0.05$) (Table 3).

No statistically significant correlations were found between Trait Anger or Anger Expression Style scores and alcohol use, gender, employment status, income level, or smoking behavior ($p>0.05$). The Anger Out subscale was significantly higher among university graduates compared with individuals with lower educational levels ($p<0.05$). Similarly, the Anger In subscale was significantly higher in patients with a documented psychiatric history ($p<0.05$).

Clinical outcomes, follow-up duration, and adherence to rehabilitation are summarized in Table 4. There were no statistically significant differences between the groups in any of these parameters ($p>0.05$).

Table 2. Demographic and injury-related characteristics of the two study groups. Values that exhibit significant difference ($p<0.05$) are bolded

Parameters	Group A (n=30)	Group B (n=18)	p value
Age Years: mean (max-min)	35.43 (20-56)	46.44 (25-62)	**0.001**
Gender: woman/man	7/23 23.3%/76.7%)	2/16 (11.1%/ 88.9%)	0.451
Dominant side involvement number (percent)	27 (90%)	2 (11%)	**0.001**
Number of injured tendons	7.03±2.69 (3-11)	6.33±2.97 (3-11)	0.406
Number of injured nerves	1.26±0.44 (1-2)	1.27±0.46 (1-2)	0.935
Number of injured arteries	0.87±0.62 (0-2)	0.83±0.51 (0-2)	0.850
Marital status/married (%)	63.3%	88.9%	0.085
Alcohol usage	6 (20%)	3 (16.7%)	1.000
Substance usage	0 (0%)	1 (5.6%)	0.375
History of psychiatric illness	4 (13.3%)	1 (5.6%)	0.637
History of similar trauma	3 (10%)	0 (0%)	0.282
Smoking	19 (63.3%)	8 (44.4%)	0.240
Education status/high school + university graduate	14 (46.7%)	5 (27.8%)	0.235

Min: Minimum, Max: Maximum

Table 3. Results of two study groups regarding anger scales

Trait Anger and anger expression style scales	Group A (n=30) (Mean ± SD)	Group B (n=18) (Mean ± SD)	p value
Trait Anger	17.73±4.6	16.94±4.3	0.543
Anger Out	15.30±4.9	14.33±4.1	0.522
Anger In	13.20±3.8	12.61±2.6	0.748
Anger Control	23.03±4.8	25.11±3.8	0.200

SD: Standard deviation

Table 4. Study group results according to the follow-up process and outcomes. There were no significant differences between the groups in relation to these factors

Parameters	Group A (n=30)	Group B (n=18)	p value
Follow-up time months: mean (min-max)	77.73 (23-135)	70.28 (18-148)	0.524
Grip strength (kg) mean (min-max)	29.10 (5-54)	28.56 (8-56)	0.892
% Grip strength of the contralateral hand	73.72%	67.34%	0.263
QDASH mean (min-max)	7.41 (0-65.9)	11.1 (0-27.3)	0.282
Number of patients not attend at least one scheduled postoperative rehabilitation appointment	7 (23.3%)	1 (5.6%)	0.229

Min: Minimum, Max: Maximum

Discussion

Our findings demonstrated significant differences between the groups regarding age and dominant-hand involvement. Patients injured by punching glass were younger, with most injuries affecting the dominant hand. These results are consistent with previous studies, which report that 78-92% of glass-punching injuries occur in young men and that 70-94% involve the dominant hand (5,7,13-16). The predominance of such injuries in young males may be related to intermittent explosive disorder, a psychiatric condition characterized by uncontrolled violent impulses leading to self-harm and aggression (14,16). By contrast, patients with work-related injuries more often sustained trauma to the non-dominant hand, which reflects occupational patterns described in the literature (17-21).

With respect to anger measures, we observed no statistically significant differences in Trait Anger, Anger Out, Anger In, or Anger Control scores between the two groups. This finding is consistent with Kural et al. (22), who also reported no significant differences in anger scales among patients with fifth metacarpal neck fractures. However, other studies have demonstrated higher levels of anger, impulsivity, and psychological distress in patients with self-inflicted hand injuries (9,13,23). These discrepancies may reflect differences in study design or patient reporting behaviors, as underreporting, social desirability bias, and regret following impulsive actions may all influence how patients complete anger questionnaires (24). A potential explanation for the absence of significant differences in anger scale outcomes among patient cohorts in our study may be attributed to the patients' tendency to give limited responses to the scales.

Alcohol use has been strongly associated with glass-related hand injuries in numerous studies, with reported prevalence ranging from 15.5% to 100% (6,13,15,25-27). Alcohol consumption is frequently cited as a contributing factor to impulsive behaviors, including punching glass, and is often considered a major risk factor for intentional upper extremity injuries. In our cohort, however, alcohol use was comparatively low and did not differ significantly between groups. This finding likely reflects the influence of cultural and religious norms in our population, where alcohol consumption is generally less common than in many of the regions where earlier studies were conducted. The comparatively low prevalence of alcohol use may therefore help explain the discrepancy between our findings and those of previous reports.

Similarly, psychiatric illness and drug use have been highlighted in the literature as important risk factors for repeated intentional injuries, particularly in younger male populations (14,28). In our study, no significant differences were found between the groups regarding psychiatric history or substance use. It should be noted, however, that information on drug use was based on self-reports rather than laboratory confirmation, which may have led to underreporting due to social stigma and legal concerns. This limitation should be considered when interpreting our results, as undetected substance use could potentially confound the relationship between psychiatric status, impulsivity, and the risk of intentional injury.

No significant difference was found between the two groups regarding their psychiatric disorder history. This result may be attributed to the limited sample size of patients in our investigation, highlighting the necessity for larger case series studies. The administration of treatment to patients with a previous psychiatric disorder may have resulted in a decrease in their Anger Out scores (29). Nonetheless, those with histories of psychiatric disorder had a considerably higher score on the Anger In subscale. The interdependent correlation among alcohol use, drug abuse, and mental disorders as predisposing factors for intentional injury should not be disregarded, and individuals seeking medical care in the emergency department due to intentional injuries should be assessed within this framework.

Tendons and neurovascular structures are the most commonly affected components in wrist injuries, often requiring multiple surgeries and prolonged rehabilitation (13,16). Clinical outcomes and hand function are also influenced by psychological factors such as anger and impulsivity (28). Patients injured by punching glass are typically younger and more often sustain dominant-hand injuries, which may result in greater long-term functional loss compared with accidental injuries (5). Prior studies have reported worse QDASH scores and higher discontinuation rates in intentional injury groups (9,28). While some research has suggested lower educational attainment among patients with punching-glass injuries (16), our study found no statistically significant differences in education level, QDASH scores, or rehabilitation compliance between groups. The slightly higher education level observed in the intentional injury group may reflect the predominance of manual laborers in the accident group.

Furthermore, we observed that the Anger Out subscale scores were higher among individuals with university degrees. Their elevated levels of knowledge may result in more unbiased responses on the scale. The absence of a statistically significant difference in postoperative rehabilitation compliance across the study groups may be ascribed to elevated educational attainment, rapid remorse experienced following impulsive behavior in a fit of anger within the intentional damage group.

Study Limitations

The primary limitation of this study was the relatively small sample size, which may have reduced the statistical power and limited the generalizability of the findings. Another limitation is the potential response bias in patient-reported questionnaires. In addition, the absence of routine laboratory testing for drug and alcohol use, with complete reliance on self-reported data, may have introduced further bias.

Conclusion

Patients injured by punching glass are predominantly young men, most with injuries to the dominant hand, and elevated scores on the Trait Anger, Anger Out, and Anger In scales. Because urgent surgical intervention is often required, preoperative psychiatric evaluation is rarely feasible. These patients should therefore be approached from a biopsychosocial perspective during postoperative follow-up, rehabilitation, and potential reoperations. Close collaboration among psychiatrists, hand surgeons, and hand therapists is essential to optimize evaluation and treatment planning.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (approval number: E-10840098-772.02-5409, date: 01.09.2023).

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

Footnotes

Authorship Contributions: Surgical and Medical Practices - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Concept - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Design - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Data Collection or Processing - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Analysis or Interpretation - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Literature Search - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.; Writing - K.U., E.A., H.K.U., Z.M.A., K.G., M.M.E.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 318-21
DOI: 10.4274/imj.galenos.2025.95580

Immunization While Hospitalization; Can It Be Opportunity for Childhood Immunization?

Büşra Tetik Dinçer[1], Şebnem Apaydın[2], Zeynep Begüm Baysal Kaya[2], Aybike Koç[2], Hasan Sinan Uslu[3], Ali Bülbül[3], Gizem Kara Elitok[2]

[1]University of Health Sciences Türkiye, Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, Clinic of Pediatrics, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Pediatrics, Division of Neonatology, İstanbul, Türkiye

ABSTRACT

Introduction: Vaccination is an important public health practice that protects individuals as well as the general population from infectious diseases. Publications have examined the effects of vaccination practices, on vaccination rates in children hospitalized for other reasons. The present study aimed to evaluate opportunistic vaccination rates in hospitalized children.

Methods: In the present study, children who were consulted for vaccination at the well-child clinic during hospitalization between 2015-2022, were retrospectively evaluated. Patients who could not be vaccinated because they did not comply with pre-vaccine administration checklist were excluded from the study. Patients were examined in three groups: routine, delayed, and risk groups. Patients were evaluated according to demographic, clinical, and vaccine characteristics.

Results: Of the 971 patients included in the study, 480 (49.4%) were female and the median age was 0 (range 0-18). Five hundred fifty-four (57.1%) of the patients were premature infants who were referred from the neonatal intensive care unit. A total of 1792 doses of vaccine were administered to the patients included in the study (677 routine vaccinations, 735 delayed vaccinations, and 380 risk group vaccinations). The most frequently administered vaccine was hepatitis B vaccine, with 975 (54.4%) doses. It is observed that delayed vaccination, and risk group vaccinations increased proportionally in the following years ($p<0.001$).

Conclusion: Hospitalizations can be seen as vaccination opportunities for children. Having units in hospitals that will administer vaccines to inpatients, will contribute to the vaccination rates in children.

Keywords: Child, immunization, inpatient, missed opportunity, vaccine

Introduction

The aim of vaccination is to protect individuals and societies from diseases and the risks that these diseases may cause (1). It is reported that 21% of deaths under the age of 5 are due to vaccine-preventable causes such as lower respiratory tract infections, meningitis, and measles (2). According to the World Health Organization data, 3.5-5 million deaths caused by infectious diseases such as diphtheria, tetanus, pertussis, influenza, and measles are prevented each year with vaccination. The fact that vaccination has a social protective effect on unvaccinated individuals and that this effect is correlated with the vaccination rate emphasizes the need to increase vaccination rates (3). An individual's visit to a health institution for any reason is an opportunity to complete missing vaccinations and to administer vaccines that are due. There are publications recommending that the vaccination status of all children be evaluated at every health institution visit (4,5). In this study, we aimed to emphasize the contribution of hospitalization in evaluating missed vaccination opportunities by examining patients who were hospitalized for various reasons in our hospital and consulted for vaccination at the well child clinic.

Methods

This descriptive, cross-sectional study included patients aged 0-18, who were consulted for vaccination at the well child clinic of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital between 2015-2022, and vaccinated while hospitalized. Consultations requested for vaccination from the well child clinic were examined retrospectively: the hospital database was used to investigate the patients' diagnoses, reasons for vaccination, vaccines administered,

Address for Correspondence: Büşra Tetik Dinçer MD, University of Health Sciences Türkiye, Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, Clinic of Pediatrics, Ankara, Türkiye
E-mail: buusratetik@gmail.com **ORCID ID:** orcid.org/0009-0003-9604-201X

Cite this article as: Tetik Dinçer B, Apaydın Ş, Baysal Kaya ZB, Koç A, Uslu HS, Bülbül A, et al. Immunization while hospitalization; can it be opportunity for childhood immunization? İstanbul Med J. 2025; 26(4): 318-21

Received: 26.12.2024
Accepted: 07.10.2025
Publication Date: 12.11.2025

and which unit requested the consultation for vaccination. Examination of the patients' vaccination cards and vaccines registered in the Vaccine tracking system was used to access previous vaccination records. The obtained data were recorded. Vaccination status was individually evaluated according to the National Immunization Program Schedule and risk group vaccination requirements.

Patients were divided into three groups: routine vaccination, delayed vaccination, and risk group vaccination:

1- Routine vaccination group: Patients whose age-appropriate vaccination time came according to the National Immunization Program Schedule.

2- Delayed vaccination group: Patients whose routine vaccination time came according to the National Immunization Program Schedule but who were not vaccinated without being in the risk group.

3- Risk group: Those who were vaccinated in addition to the National Immunization Program Schedule due to reasons such as prematurity and/or low birth weight, chronic diseases (e.g., malignancies, transplantation, and immunosuppressive treatments), and conditions predisposing to encapsulated bacterial infections (e.g., asplenia, post-splenectomy status, immunosuppressive diseases, complement deficiencies, and antibody production disorders).

Patients who were consulted at the well-child clinic for vaccination but were not vaccinated according to the pre-vaccine administration checklist were excluded from the study (6).

The present study was conducted in accordance with the Helsinki Declaration and was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (approved number: 4425, date: 11.06.2024).

Statistical Analysis

Statistical analysis were performed using SPSS version 25.0 and TURCOSA. Categorical data were expressed as numbers and percentages, while continuous data were expressed as median and range. Chi-square tests (Pearson chi-square, Fisher's exact test, etc.) were used to compare categorical data. All p-values were two-sided, and the results were evaluated using a significance level of $p<0.05$ with a 95% confidence interval.

Results

A total of 971 patients were included in the study. Four hundred eighty (49.4%) of the patients were female and the median age was 0 (range 0-18). Seven hundred twenty nine (74.6%) of the patients were between 0-12 months old. Five hundred fifty four (57.1%) of the patients were premature infants from the neonatal intensive care unit (ICU) (Table 1).

A total of 1,792 doses of vaccine were administered to the patients included in the study between 2015 and 2022. Of these doses, 677 were routine vaccinations, 735 were delayed vaccinations, and 380 were risk group vaccinations. When the vaccination trend was evaluated between 2015-2022, delayed vaccinations and risk group vaccinations were seen to increase proportionally, while routine vaccination decreased ($p<0.001$) (Table 2).

The most frequently administered vaccine was hepatitis B vaccine with 975 (54.4%) doses. Pneumococcal conjugate vaccine was the second most frequently administered vaccine, administered, with 319 (17.8%) doses, and pentavalent vaccine (DaBT-IPA-Hib) the third, with 302 (16.9%) doses. The number of vaccine applications by year is given in detail in Table 3.

Discussion

In our study, among the 971 patients evaluated, a total of 1,792 vaccine doses were administered, of which 677 were routine, 735 were delayed, and 380 were risk group vaccinations. It was determined that only one fifth of the vaccines administered to children during hospitalization were given because the children were in the risk group, and the vast majority were delayed and routine vaccinations. It has been reported that vaccination rates have decreased in our country and the world for

Table 1. Demographic and clinicopathologic features of the participants

Variables		n	%
All patients		971	100
Age (median 0, range 0-18)	0-12 months	729	75
	12-72 months	103	10.6
	6-13 years	91	9.3
	14-17 years	48	4.9
Gender	Female	480	49.4
	Male	491	50.6
Diagnosis	Prematurity	554	57.1
	Respiratory diseases	109	11.2
	Renal diseases	65	6.7
	Malignancy	58	6
	Gastrointestinal diseases	49	5
	Neurological diseases	47	4.8
	Metabolic diseases	30	3.1
	Endocrinological diseases	22	2.2
	Cardiovascular diseases	17	1.7
	Post-splenectomy	12	1.2
	Infectious diseases	8	1

Table 2. Yearly distribution of reasons for vaccination

Variables	Routine	Delayed	Risk group	p-value
2015	142	7	22	**<0.001**[a]
2016	115	11	40	
2017	71	103	65	
2018	47	134	49	
2019	49	141	61	
2020	96	128	36	
2021	81	75	36	
2022	76	136	71	
Total (1792)	**677**	**735**	**380**	

[a]Chi-square test

Table 3. Vaccinations administered to pediatric patients during hospitalization between 2015-2022

Vaccines	2015	2016	2017	2018	2019	2020	2021	2022	Total vaccine count (n=1792)
Hepatitis B	118	113	131	102	114	116	112	169	975 54.4%
DPT	24	20	42	44	45	54	35	38	302 16.9%
CPV	24	21	46	53	52	50	31	42	319 17.8%
Hepatitis A	3	5	14	15	27	24	10	15	113 6.3%
MMR	0	2	4	4	5	8	0	7	30 1.7%
Varicella zoster	0	1	2	6	4	7	0	5	25 1.4%
Meningococcus	0	1	0	3	3	1	3	4	15 0.8%
Oral polio vaccine	0	0	0	3	1	0	1	0	5 0.3%
BCG	1	1	0	0	0	0	0	1	3 0.2%
Pneumococcus	0	2	0	0	0	0	0	2	4 0.2%
Influenza	1	0	0	0	0	0	0	0	1 0.1%

DPT: Diphteria pertussis tetanus, CPV: Conjugated pneumococcus vaccine, MMR: Measles, mumps and rubella, BCG: Bacillus Calmette-Guérin

various reasons in recent years (7). The factors that cause the decrease in vaccination rates can be divided into two groups: health institution and personnel, and family and community-based reasons. Examples of missed vaccination opportunities originating from health institutions include lack of equipment and vaccines, lack of information about vaccination and incorrect contraindications, and avoidance of multiple vaccines at the same time. Examples of missed vaccination opportunities originating from health institutions include lack of education, misinformation, and beliefs originating from families and society (8). Hospitalization can be seen as an opportunity to reach more children and adolescents who have missed vaccinations, thereby contributing to increasing the effectiveness of vaccination programs (9).

Mihalek et al. (9)'s study showed that children who were hospitalized had low vaccination rates compared to the general population. Weddle and Jackson (10) study found that 92% of patients who were hospitalized received age-appropriate vaccines, and the most missed vaccines were influenza (67%), meningococcal (57%), hepatitis A (48%), and varicella (38%). In a recent retrospective cohort study by Bryan et al. (11), the most common vaccines administered to hospitalized patients were the hepatitis B birth dose and influenza vaccine. In our hospital, all newborns are given hepatitis B birth doses by the neonatal clinic. Therefore, we did not include routine hepatitis B doses administered in the delivery room in our study, although the most commonly administered vaccine was it.

In a study published in 2020 by Diallo et al. (12), it was reported that in 275 children aged between 6 and 18 months and affected by type 1 diabetes, human immunodeficiency virus infection, Down syndrome, cystic fibrosis, or neurological diseases, the coverage of diphtheria-tetanus-pertussis, polio, and hepatitis B vaccines approached 85% at 24 months; measles-mumps-rubella coverage was 62%, and seasonal influenza coverage was 59%. There was also heterogeneity among children with different chronic diseases. In the present study, regardless of the risk group, it was observed that the hepatitis B vaccine was the second and third most frequently administered vaccine, followed by the conjugated pneumococcal and pentavalent vaccines, in all groups.

Various invasive infectious diseases, including vaccine-preventable infectious diseases, pose a higher risk for children with chronic diseases. In a 2023 study, 14 Italian children's hospitals were evaluated concerning their vaccination practices. According to this study, the services where vaccination is offered more frequently to inpatients are general pediatrics, neonatology, pediatric hematology and oncology, pediatric endocrinology, pediatric cardiology and pediatric infectious diseases (range, 58% to 83%). While 58% of the hospitals that provide vaccination reported <500 vaccinations/year, 17% reported >2,000/year (13). In the present study, it was determined that 1792 doses of vaccine were administered to 971 children while they were hospitalized in our hospital. Again, it was determined that the unit that requested the most consultation for vaccination, was the neonatal ICU, with 59% (n=1058). The other units that requested the most consultation were neonatal intensive care, general pediatrics, pediatric hematology and oncology, and pediatric infectious diseases. This study emphasizes the benefit of adding a vaccination center to in-hospital well-child clinics. It ensures children at risk of being behind on vaccines receive proper immunization.

Study Limitations

One limitation of our study is its retrospective design. Additionally, not all hospitalized children were assessed for vaccination status, as some patients admitted during the study period were not evaluated for vaccination in the healthy child clinic.

Conclusion

It is known that vaccination rates have decreased in recent years due to several factors. In the present study, it was determined that the majority of vaccines administered to children while they were hospitalized were delayed routine vaccinations. By administering vaccines during hospitalization, children in the risk group who need vaccination, as well as those with delayed and routine vaccinations, can be covered. According to the results of the present study, hospitalization can be seen as an opportunity for vaccination, and thus, there should be units in hospitals where vaccinations can be administered.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (approved number: 4425, date: 11.06.2024).

Informed Consent: Retrospective study.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 322-8
DOI: 10.4274/imj.galenos.2025.59458

The Effect of Rocuronium Dosage on Intubation Conditions in Liver Transplant Recipients

Sümeyye Koç İçlek[1], Duygu Demiröz[2], Yusuf Ziya Çolak[2], Neslihan Altunkaya Yağcı[2], Oya Olcay Özdeş[3], Mehmet Ali Erdoğan[4], Nurçin Gülhaş[2], Mahmut Durmuş[4]

[1]Muş State Hospital, Clinic of Anesthesiology and Reanimation, Muş, Türkiye
[2]İnönü University Faculty of Medicine, Department of Anesthesiology and Reanimation, Malatya, Türkiye
[3]Battalgazi State Hospital, Clinic of Anesthesiology and Reanimation, Malatya, Türkiye
[4]Medeniyet University Faculty of Medicine, Department of Anesthesiology and Reanimation, İstanbul, Türkiye

ABSTRACT

Introduction: Neuromuscular blockers (NMB) play an important role in improving conditions in orthotopic liver transplantation (OLT). Depending on clinical conditions, diseases, and pharmacological interactions, the effective NMB dose for complete NMB varies. Our study investigated the effects of rocuronium used during rapid sequence intubation. The effects of this drug on onset of action and intubation conditions were studied in a control group and in an OLT patient group.

Methods: The study is prospective, involving 90 patients over the age of 18. The 45 patients scheduled to undergo OLT were assigned to Group 1, while the 45 patients without liver dysfunction scheduled to undergo a 4-6-hour surgery under general anesthesia were assigned to Group 2. Groups were dosed with 1.2 mg/kg rocuronium based on ideal body weight, and the effect on the time to reach a train-of-four (TOF) value of zero (TOF 0), time to intubation scores, and hemodynamic parameters was evaluated.

Results: The demographic data across the groups were comparable. No significant differences were observed between the groups concerning TOF 0 time ($p=0.806$), intubation times ($p=0.987$), and intubation scores ($p=0.898$). However, when evaluating OLT patients individually, a statistically significant correlation was found between TOF 0 time and Child score ($p=0.029$, $p<0.05$).

Conclusion: In patients with end-stage liver disease undergoing OLT, administering rocuronium at a dosage of 1.2 mg/kg based on ideal body weight, during rapid sequence intubation results in sufficient intubation conditions. Furthermore, there were no delays noted in the onset of rocuronium's action.

Keywords: Orthotopic liver transplantation, neuromuscular block, rocuronium, rapid serial intubation, ideal body weight

Introduction

Orthotopic liver transplantation (OLT) is the definitive treatment modality for end-stage liver disease, regardless of its origin. Neuromuscular block (NMB) provides better surgical conditions in all laparotomy and laparoscopic operations including OLT (1). Succinylcholine and rocuronium are preferred as neuromuscular muscle relaxant agents for rapid sequence induction. There are conditions that limit the use of succinylcholine, one of which is hyperkalaemia (2). The ability of sugammadex to rapidly reverse the activity of rocuronium has led it to be preferred as an alternative agent to succinylcholine (3,4). The pharmacokinetics and pharmacodynamics of rocuronium bromide may change in patients with hepatic dysfunction, which may result in a longer elimination half-life and unpredictable onset of action. The literature contains studies related to the duration of action of rocuronium in patients undergoing OLT, but few studies address the onset of action of rocuronium and its effect on intubation conditions (5,6).

In our literature review, the duration of action of NMBs in OLT patients was evaluated, but studies of the onset of effect of rocuronium dose and intubation conditions are limited. In our study, we aimed to evaluate the effects of NMB on onset of action and intubation conditions by administering rocuronium according to the ideal body weight in patients undergoing OLT and those with normal liver function tests.

Methods

This study employs a prospective observational design and is conducted in accordance with the Helsinki-2013 Declaration. Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (protocol number: 2022/61, date: 29.06.2022).

Address for Correspondence: Oya Olcay Özdeş MD, Battalgazi State Hospital, Clinic of Anesthesiology and Reanimation, Malatya, Türkiye
E-mail: oyayiilmaz@hotmail.com **ORCID ID:** orcid.org/0000-0002-5436-3654

Cite this article as: Koç İçlek S, Demiröz D, Çolak YZ, Altunkaya Yağcı N, Özdeş OO, Erdoğan MA, et al. The effect of rocuronium dosage on intubation conditions in liver transplant recipients. İstanbul Med J. 2025; 26(4): 322-8

Received: 31.08.2025
Accepted: 14.10.2025
Publication Date: 12.11.2025

To determine the required sample size, a power analysis was conducted, indicating that a minimum of 41 patients from each group, totaling 82 patients, should be included to identify a significant difference, with a type 1 error rate (alpha) of 0.05, a statistical power (beta) of 0.8, and an effect size of 0.10.

In this prospective observational study, two groups were defined: patients scheduled for liver transplantation (Group 1) and patients without liver dysfunction undergoing abdominal surgery lasting 4-6 hours (Group 2). Although the study employed a prospective observational design, a block and stratified randomization approach was applied to ensure balance between the groups and to minimize selection bias.

Randomization was performed using computer-generated random sequences with a 1:1 allocation ratio. To reduce predictability, permuted variable block sizes (4, 6, and 8) were used. To maintain clinical balance between groups, stratified randomization was performed according to the following variables:

Child-Pugh class: A/B vs. C

Body mass index (BMI) category: <25 kg/m², 25-30 kg/m², and >30 kg/m²

Mallampati score: I-II vs. III-IV

Allocation concealment was maintained using a centralized electronic randomization system; if this was unavailable, sequentially numbered, opaque, sealed envelopes were used. Group assignments were concealed from the clinicians administering the study interventions and from the outcome assessors.

After obtaining written informed consent from all participants, randomization was completed, and a total of 90 patients were included in the study, with 45 patients in each group.

Patients with confirmed renal dysfunction, those diagnosed with neuromuscular diseases, and individuals with a history of malignant hyperthermia were excluded from the study. Additionally, patients with a BMI exceeding 35 kg/m², as well as pregnant or breastfeeding women, were not included. Those who chose not to participate and 16 patients who underwent surgery in emergency situations were omitted from the analysis. In our study, patients who were excluded due to emergency surgery were not included in the analysis because of missing demographic and clinical data. All patients received information regarding the study's details and provided written informed consent. Ultimately, a total of 90 patients were enrolled in the study, with 45 patients in each group (Figure 1).

Demographic information for the patients, such as age, gender, and height, was carefully documented. Body weight, ideal body weight, and BMI were measured using bioelectrical impedance analysis with the Tanita BC-418 MA device (Tokyo, Japan). Significant medical scores, including the American Society of Anesthesiologists (ASA) score and Mallampati score, were recorded alongside preoperative laboratory values, which included creatinine (mg/dL), albumin (mg/dL), platelet count, international normalized ratio (INR), and total bilirubin (mg/dL). Furthermore, the Child-Turcotte-Pugh (CHILD) and Model for End-Stage Liver Disease (MELD) scores were calculated and documented. The presence and severity of encephalopathy were also evaluated and noted (7).

Anaesthesia Management

Patients were taken to the operating room without premedication. Routine non-invasive blood pressure, pulse, oxygen saturation (SpO_2) and electrocardiography monitoring were performed. In addition, Bispectral index (BIS) (Masimo SET® Rainbow, Masimocorp. Irvine, CA) was monitored to measure the depth of anesthesia and NMB was monitored with train-of-four (TOF) TOF-Watch SX (OrganonIreland, a division of MSD Swords, Dublin, Ireland).

Our study was conducted in a single-blind design. Due to its prospective observational nature, it was not feasible to achieve complete blinding of the operators. Nevertheless, the assessment of intubation scores was performed by an independent and experienced anesthesiologist who was blinded to the group allocation, thereby minimizing potential bias in the subjective measurements. Furthermore, it was clearly stated in the study that the observer assessing the intubation scores was blinded; the operators were not involved in data analysis; and all measurements were carried out according to a standardized protocol.

Patients were preoxygenated with 100% oxygen through a face mask for 3 minutes. Anesthesia induction was facilitated by the intravenous (IV) administration of thiopental at a dose of 3-5 mg/kg, along with 1 mg/kg of lidocaine and 1-2 µg/kg of fentanyl. After achieving an appropriate depth of anesthesia, indicated by a BIS value between 40-60, rocuronium bromide (CURON 50 mg/5 mL, Gensenta İlaç Sanayi ve Ticaret A.Ş.) was administered IV at a dose of 1.2 mg/kg based on the ideal body weight. Following anesthesia induction, neuromuscular function was monitored using a TOF-Watch SX device equipped with an acceleromyography transducer, which was placed on the distal phalanx of the thumb. The ulnar nerve was stimulated at the wrist, and repeated TOF assessments were conducted at 15-second intervals.

The time taken for the TOF value to reach zero was recorded as time to TOF zero. Female patients were intubated using endotracheal tubes with an internal diameter of 7-7.5 mm, whereas male patients were intubated with tubes ranging from 8-8.5 mm; all procedures were conducted by an experienced anesthesiologist. Proper placement of the endotracheal tube was confirmed through auscultation and monitoring of end-tidal carbon dioxide ($ETCO_2$) levels. Intubation times and conditions were evaluated using the Helbo-Hansen Raulo and Trap-Anderson scoring system (8). For patients who required additional rocuronium, a supplementary dose of 0.1 mg/kg was given, and these doses were carefully documented.

Patients undergoing OLT underwentleft radial artery cannulation for continuous blood pressure monitoring and blood sampling after intubation. Right jugularveincatheterization was also performed for centralvenous pressure measurement and vasopressortherapy. Body temperature of all patients was monitored by nasopharyngealprobeinsertion and body temperature was not lowered below 37 °C by covering with a thermalblanket and warming all infusion fluids (Hot Line® SIMS MedicalSystemInc, Rocklan, MA, USA; Fluido® Pressure Chamber, TSCI, Amersfoort, Netherland).

Anesthesia maintenance was achieved using a combination of 2% sevoflurane and rocuronium administered at a continuous rate of 0.1 mg/kg/hour, alongside intermittent bolus doses of fentanyl, in an oxygen-air mixture. Patients were placed on mechanical ventilation to maintain $ETCO_2$ levels within the target range of 30 to 40 mmHg. To assess hemodynamic parameters, heart rate (HR), mean arterial pressure, systolic arterial pressure, diastolic arterial pressure, and SpO_2 levels were measured at multiple time intervals: before anesthesia, following induction, after intubation, and subsequently at 1, 5, 15, and 30 minutes after intubation.

In Group 1 patients who underwent OLT, the amount of ascites (mL) drained during surgery was recorded, and the study was terminated.

Statistical Analysis

IBM SPSS Statistics 22 program was used for statistical analysis while evaluating the findings obtained in the study. The parameters' compliance with a normal distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency,) Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons between two groups of parameters that were not normally distributed. The chi-square test, Fisher's exact chi-square test, Fisher Freeman Halton exact chi-square test, and continuity (Yates) correction were used to compare qualitative data. Pearson correlation analysis was used to examine the relationships between parameters that conform to a normal distribution, and Spearman's rho correlation analysis was used to examine the relationships between parameters that do not conform to a normal distribution. Significance was evaluated at the $p<0.05$ level.

Results

Among the 90 patients involved in the study, 44 (48.9%) were female and 46 (51.1%) were male. The average age of the patients was 50.12±12.10 years. There were no significant differences between the groups regarding demographic factors such as age, gender, height, weight, ideal weight, average BMI, and Mallampati scores ($p>0.05$) (Table 1).

There were no statistically significant differences between the groups regarding rocuronium administration, duration until the TOF reached 0, and intubation times ($p>0.05$). Notably, only one patient (2.2%) in Group 1 required an additional dose, while none in Group 2 did ($p>0.05$). Additionally, there was no statistically significant difference in intubation scores between the groups ($p>0.05$), with excellent intubation scores reported in 71.1% of Group 1 and 73.3% of Group 2 (Table 2).

Table 1. Evaluation of demographic data [mean ± SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Age (years)		51.62±13.1	48.62±10.96	[1]0.242
Height (cm)		165.2±9.29	165.47±9.17	[1]0.891
Total weight (kg)		73.87±11.81	72.87±11.65	[1]0.687
Ideal weight (kg)		59.87±10.21	59.11±9.97	[1]0.723
BMI		27.07±4.55	26.82±3.73	[1]0.781
Gender (%)	Female	19 (42.2%)	25 (55.6%)	[2]0.292
	Male	26 (57.8%)	20 (44.4%)	
Mallampati	I	11 (24.4%)	28 (62.2%)	[3]0.001*
	II	24 (53.3%)	15 (33.3%)	
	III	10 (22.2%)	2 (4.4%)	

[1]: Student t-test, [2]: Continuity (Yates) correction, [3]: chi-square test, *p<0.05, SD: Standard deviation, BMI: Body mass index

Table 2. Comparison of neuromuscular blocker use intubation score between groups [mean ± SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Rocuronium dose (mg)		72.51±13.12 (75)	72.0±12.08 (70)	[1]0.616
TOF 0 time (seconds)		117.44±62.28 (109)	112.38±51.22 (108)	[1]0.806
Intubation time (seconds)		14.73±7.76 (12)	14.89±7.45 (13)	[1]0.987
Additional dose	None	44 (97.8%)	45 (100%)	[2]1.000
	Done	1 (2.2%)	0 (0%)	
Intubation score	Perfect	2 (71.1%)	33 (73.3%)	[3]0.898
	Good	10 (22.2%)	10 (22.2%)	
	Middle	3 (6.7%)	2 (4.4%)	

[1]: Mann Whitney U test, [2]: Fisher's exact test, [3]: Fisher Freeman Halton exact test, SD: Standard deviation, TOF 0: Train-of-four value of zero

In the analysis of patients in Group 1, a statistically significant association was identified between the TOF 0 time and Child score (p=0.029) (Figure 2). However, no positive correlation was found between TOF 0 time and either ascites or MELD scores (p>0.05). Additionally, the evaluation of the relationship between intubation time, intubation scores, ascites, the Child-Pugh score, and MELD scores revealed no statistically significant findings (p>0.05) (Table 3).

Table 4 presents the results of the multivariable linear regression analysis assessing the factors influencing TOF 0 duration. In the full model, none of the predictors reached statistical significance (p>0.05). The intercept indicates the baseline predicted TOF 0 duration of approximately 195 seconds when all predictors are held at zero.

Although BMI showed a negative association with TOF 0 duration (β=-2.66 s per unit increase, p=0.121), this effect did not reach statistical significance in the full model. Other variables, including age, ASA class, Mallampati score, Child score, MELD score, albumin, INR, total bilirubin, and encephalopathy, also showed no significant independent effects.

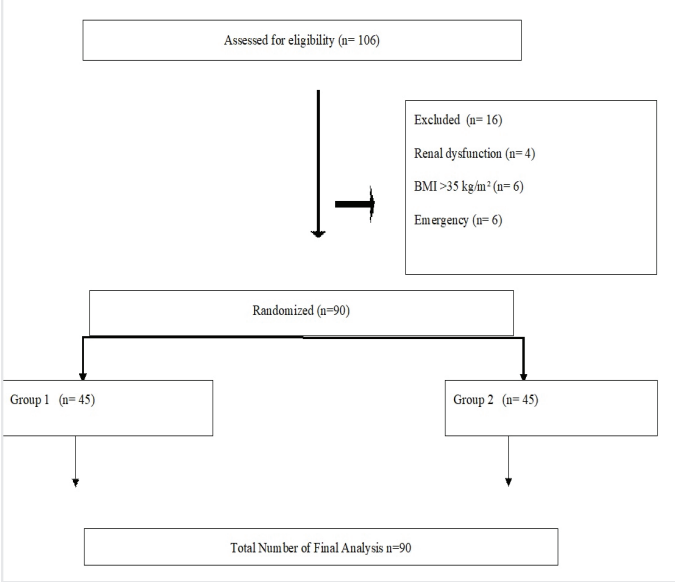

Figure 1. CONSORT flow diagram of this study
BMI: Body mass index

High collinearity was observed among liver-function-related variables (Child score, MELD score, and albumin), which may have reduced the precision of their individual estimates. The relatively low R^2 (0.115) suggests that most of the variability in TOF 0 duration remains unexplained, indicating the potential influence of additional clinical or perioperative factors not included in the current model.

When examining hemodynamic parameters, Group 1 exhibited mean HRs that were significantly lower than those in Group 2 prior to anesthesia, and at the following time points: after intubation, and at 1, 5, 15, and 30 minutes following intubation (p<0.05) (Table 5).

Discussion

In our study, we compared patients with end-stage liver failure undergoing OLT, to those with normal liver function. We found that the duration of action of the NMB, as well as intubation times and conditions, was similar when administering rocuronium at a dose of 1.2 mg/kg based on ideal body weight. Our findings suggest that this dosage of rocuronium can effectively ensure adequate intubation conditions for patients undergoing OLT.

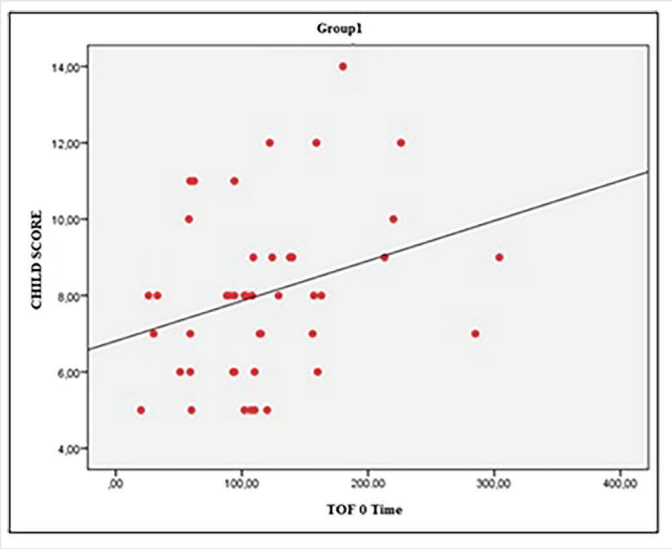

Figure 2. Relationship between Child score and TOF 0 time
TOF 0: Train-of-four value of zero

Table 3. Correlation of rocuronium. TOF 0 duration. Intubation duration and intubation score with a Spearman's rho correlation analysis *p<0.05
Acid, Child and MELD score in Group 1

		Rocuronium dose	TOF 0 duration	Intubation duration	Intubation score
Acid	r	0.064	0.150	-0.012	-0.039
	p	0.674	0.325	0.938	0.800
Child score	r	0.273	0.326	-0.017	-0.029
	p	0.070	0.029*	0.912	0.851
MELD score	r	0.334	0.089	0.083	-0.014
	p	0.025*	0.560	0.588	0.927

Spearman's rho correlation analysis *p<0.05, TOF 0: Train-of-four value of zero, MELD: Model for End-Stage Liver Disease score

Table 4. Multivariable regression analysis for TOF 0 duration

Variable	Coefficient (β)	Std. error	t value	p value	95% CI lower	95% CI upper
Intercept	194.57	92.64	2.10	0.039	10.14	378.99
Age (years)	-0.08	0.59	-0.14	0.892	-1.24	1.08
Sex (male=1)	+16.42	12.81	+1.28	0.204	-9.08	41.92
BMI (kg/m²)	-2.66	1.70	-1.57	0.121	-6.04	0.72
ASA class	-16.56	12.23	-1.35	0.180	-40.91	7.79
Mallampati	+4.60	9.82	+0.47	0.641	-14.96	24.15
Child score	+7.22	6.63	+1.09	0.280	-5.98	20.41
MELD score	-1.41	2.10	-0.67	0.504	-5.59	2.77
Albumin (g/dL)	-2.49	14.91	-0.17	0.868	-32.18	27.19
INR	+18.99	31.96	+0.59	0.554	-44.64	82.62
Total bilirubin	-0.24	2.90	-0.08	0.935	-6.02	5.54
Encephalopathy	-18.53	29.76	-0.62	0.535	-77.78	40.72

n=90, R^2=0.115, Adjusted R^2=-0.009, F-statistic=0.93 (p=0.521), TOF 0: Train-of-four value of zero, Std: Standard, CI: Confidence interval, BMI: Body mass index, ASA: American Society of Anesthesiologists, MELD: Model for End-Stage Liver Disease score, INR: International normalized ratio

Table 5. Evaluation of hemodynamic parameters [mean ± SD or number (%)]

		Group 1 (n=45)	Group 2 (n=45)	p value
Heart rate (beats/min)	Before anesthesia	78.56±13.77	86.76±16.4	0.012*
	Post induction	82.58±14.23	87.84±17.55	0.121
	After intubation	85.71±17.06	99.11±19.57	0.001*
	1. min	83.09±16.47	95.73±18.11	0.001*
	5. min	78.58±14.97	88.96±22.33	0.011*
	15. min	78.6±16.72	90.96±18.61	0.001*
	30. min	75.8±14.81	87.02±17.56	0.002*
SAP (mmHg)	Before anesthesia	137.4±28.06	140.07±24.47	0.632
	Post induction	113.36±21.86	115.71±27.55	0.654
	After intubation	122.56±25.47	146.84±29.79	0.000*
	1. min	115.09±23.52	124.42±31.46	0.115
	5. min	103.91±18.74	110.73±21.45	0.112
	15. min	98.8±21.63	107.76±18.73	0.039*
	30. min	98.71±20.21	112.4±17.03	0.001*
DAP (mmHg)	Before anesthesia	75.4±10.89	84.51±11.34	0.000*
	Post induction	66.24±15.75	76.73±13.02	0.001*
	After intubation	69.53±14.42	95.53±21.37	0.000*
	1. min	65.36±13.23	78.93±19.64	0.000*
	5. min	58.67±12.17	68.4±14.46	0.001*
	15. min	57.07±10.77	66.31±12.89	0.000*
	30. min	58.09±11.51	71.8±12.92	0.000*
MAP (mmHg)	Before anesthesia	97.73±17.92	106.24±17	0.023*
	Post induction	82.89±17.66	92.91±16.58	0.007*
	After intubation	88.87±17.55	115.44±23.78	0.000*
	1. min	84.33±17.09	96.53±24.49	0.007*
	5. min	76.16±14.67	85.76±14.66	0.003*
	15. min	74.4±13.38		0.005*
	30. min	75±13.36	87±13.39	0.000*

SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, Student t-test, *p<0.05, SD: Standard deviation, Min: Minute

Rapid serial intubation (RSII) for general anaesthesia is preferred in patients at high-risk of pulmonaryaspiration. In OLT patients, there is a decrease in oncotic pressure due to a decrease in proteins, especially albumin, and ascites accumulation, which occurs in approximately 60% of cirrhotic patients. Since ascites increases intraabdominal pressure, RSII is recommended in these patients (9). The preferred NMBs in RSII are succinylcholine and rocuronium. Since succinylcholine has side effects leading to hyperkalaemia and rapid desaturation by increasing oxygen consumption and rocuronium has no contraindication, there is ongoing debate about the choice of agent for RSII (10). We do not prefer succinylcholine because of electrolyte disturbance, and potassium elevation that may develop preoperatively and in the intraoperative period in OLT patients.

Water-soluble drugs have limited distribution volumes that are not affected by fat depots. Therefore, under certain conditions, the administration of water-soluble drugs according to actual body weight may lead to an overdose. Overdose of hydrophilic NMBs, which are frequently used in anaesthesia practice, may result in prolonged recovery and postoperative respiratory complications. Since the distribution of hydrophilic drugs is limited to lean tissue, the dose to be administered should generally be based on ideal body weight or corrected body weight. Cirrhotic liver disease and renal insufficiency also result in an increased volume of distribution and lower plasma concentrations of hydrophilic drugs, leading to a situation where the initial dose is increased but lower maintenance doses are required. It is necessary to confirm adequate laryngeal muscle relaxation by neuromonitoring and to determine whether additional doses are needed. In our patients, we used TOF-Watch SX monitoring to evaluate the duration of action of NMBs by administering rocuronium according to ideal body weight.

Several studies have compared the onset of action of NMBs in liver diseases such as liver cirrhosis and hepatoma. Khalil et al. (11) investigated the 0.6 mg/kg rocuronium dose in patients who underwent surgery due to liver disease; they emphasized that the onset of action was prolonged by approximately 45%. Another study investigated the pharmacokinetic effects of 0.6 mg/kg rocuronium in liver disease using a control group. No relationship was found between the onset of action of rocuronium and liver disease (12). In our study, rocuronium onset of action and intubation scores were similar in patients with liver failure and those with normal liver function. The discrepancy observed in the literature review may be explained by changes in patient numbers and inappropriate use of neuromonitoring methods.

Sluga et al. (13) emphasised that they found the onset time for the effect of rocuronium to be 130 seconds, using propofol and 0.6 mg/kg rocuronium in rapid sequence intubation. In another study, optimal intubation conditions were achieved after 45-60 seconds at a rocuronium dose of 0.6 mg/kg (14). In our study, the time was 117.44 seconds on average in the patient group with liver failure and 112.38 seconds, in the patient group with normal liver function, and these times were statistically similar. However, the rocuronium dose used in our study was 1.2 mg/kg, which differs from doses reported in the literature. We think that this difference may be due to the application of the rocuronium dose used in our study based on ideal body weight and the use of thiopental as an induction agent to provide haemodynamic stability, which differs from other studies. Similar studies on this subject are needed.

In our study, there was no significant correlation between TOF 0 duration and MELD score, but there was a positive and moderate correlation (32.6%) which was statistically significant correlation between the Child score and another variable (unspecified). We think that the difference in these results is because the Child score includes subjective criteria such as encephalopathy, although it has been used as a reliable method for years in determining liver reserve (15).

Cardiomyopathy, diastolic dysfunction and coronary artery disease may accompany cirrhotic liver disease and blood pressure may be normal orlow in these patients (16). The mechanism of systemic vasodilation in the pathogenesis of cirrhotic cardiomyopathy is still a matter of debate. However, it has been associated with various humoral mediators such as nitric oxide, adrenomedullin, natriuretic peptides, cytokines, hydrogen sulfide, endothelins, and endocannabinoids. Disruption of the balance in the release of these mediators causes vasodilatation. At the same time, bacterial endotoxins lead to peripheral vasodilatation by stimulating endogenous cannabinoid production (17,18). In our study, we thinkhypothesize that these reasons related to liver failure are responsible for the finding of a haemodynamically significant difference between the two groups.

Study Limitations

This study has a few limitations. First, it is a single-center study and may have a limited sample size. The generalizability of the results could be improved with a larger sample size. Additionally, OLT patients receive different drug treatments may influence the effects of rocuronium. This may make it difficult to interpret the results.

Conclusion

In patients with advanced liver failure scheduled for liver transplantation, administering rocuronium at a dose of 1.2 mg/kg based on ideal body weight appears to yield a similar onset of action to that seen in individuals with normal liver function, while also ensuring sufficient conditions for intubation. We propose that this rocuronium dosage can be safely utilizedused for anesthesia induction during OLT and rapid sequence intubation in this patient group. However, additional comprehensive studies are necessary to further validate our findings.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Malatya Clinical Research Ethics Committee (protocol number: 2022/61, date: 29.06.2022).

Informed Consent: All patients received information regarding the study's details and provided written informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.K.İ., D.D., Y.Z.Ç.; Concept - M.A.E., N.G., M.D., N.A.Y.; Design - S.K.İ., Y.Z.Ç., N.A.Y., M.A.E., M.D.; Data Collection or Processing - S.K.İ., O.O.Ö., Y.Z.Ç., M.D.; Analysis or Interpretation - D.D., N.A.Y., M.A.E., N.G.; Literature Search - D.D., N.G., O.O.Ö.; Writing - S.K.İ., D.D., O.O.Ö.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 329-34
DOI: 10.4274/imj.galenos.2025.60307

The Effect of Visfatin Levels on Blood Pressure and Cardiac Risk Factors in Patients with Acromegaly

Ömer Faruk Kuzu[1], Emre Hoca[2], Evrim Çakır[3], Hayriye Esra Ataoğlu[2]

[1]Çankırı State Hospital, Clinic of Medical Oncology, Çankırı, Türkiye
[2]University of Health Sciences Türkiye, Haseki Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Taksim Training and Research Hospital, Clinic of Endocrinology, İstanbul, Türkiye

ABSTRACT

Introduction: Acromegaly is a hormonal disorder characterized by gradual somatic changes that influence multiple bodily organs and systems. Cardiovascular complications are the primary cause of mortality in individuals with this condition. Visfatin is one of the adipocytokines whose role in obesity and metabolic diseases is controversial. This study aimed to investigate the correlation between visfatin levels and various laboratory and cardiometabolic parameters in patients diagnosed with acromegaly.

Methods: The study included 28 patients diagnosed with acromegaly, forming the patient group. A control group of 27 patients, without a history of chronic disease, was also enrolled from the patient population attending our hospital. Echocardiographic findings and 24-hour blood pressure holter results of all participants were recorded. Blood samples were obtained from the control group and the patients.

Results: Patients with acromegaly exhibited a higher proportion of females, fasting blood glucose levels, growth factor-1 levels, and left ventricular end-diastolic diameter compared to the control group. Conversely, visfatin levels were found to be lower in acromegaly patients. No correlation was identified between visfatin levels and blood pressure or other biochemical parameters in these patients. However, a positive correlation was observed specifically between left atrium diameter and visfatin levels.

Conclusion: Our study revealed that only a limited number of parameters showed a significant association with visfatin levels. Further research with a larger patient cohort is necessary to confirm these findings.

Keywords: Acromegaly, blood pressure, cardiovascular complications, visfatin

Introduction

Acromegaly is an endocrine disease with progressive somatic disorders affecting many organs and systems in the body (1). Cardiovascular system involvement, driven by elevated insulin-like growth factor-1 (IGF-1) and growth hormone (GH), is the leading cause of mortality in these patients, accounting for 60% of deaths (2). The remaining 25% of patients do not survive due to respiratory system problems, and 15% are lost due to malignancy. The most important determinant of mortality is the control of GH levels (3). The heightened risk of cardiovascular disease in acromegalic patients is linked to the frequent presence of atherosclerotic risk factors like hypertension and diabetes; however, cardiovascular involvement in acromegaly can manifest even in the absence of other risk factors (4). Cardiac hypertrophy and cardiomyopathy, directly or indirectly induced by high GH levels through IGF-1, are among the most prevalent cardiac complications in acromegaly patients (1,4). While heart abnormalities may emerge in the early stages of acromegaly, their prevalence tends to rise as patients grow older (5,6). At the time of diagnosis, echocardiographic left ventricular ejection fraction is often normal in the vast majority of patients (55-78%), but microscopic structural defects or subclinical echocardiographic findings are more likely to be present in these patients (7,8).

Adipose tissue serves various roles, including mechanical cushioning, heat production, energy and fat-soluble vitamin storage, and acting hormonally by releasing adipocytokines that regulate metabolism, eating behavior, insulin response, and inflammation (9-11). Visceral adipose tissue, located around major abdominal organs, holds greater significance than subcutaneous adipose tissue in the development of obesity-related conditions such as type 2 diabetes (T2D), cardiovascular pathologies, and diseases of the lung, liver, and kidneys, as well as cancer (11,12).

Adipocytes synthesize some adipocytokines, and some are synthesized by stromal-vascular adipose tissue components, such as preadipocytes, endothelial cells, lymphocytes, macrophages, and fibroblasts (9).

Address for Correspondence: Emre Hoca Asst. Prof., MD, University of Health Sciences Türkiye, Haseki Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye
E-mail: emrehoca89@gmail.com **ORCID ID:** orcid.org/0000-0003-4232-7362

Cite this article as: Kuzu ÖF, Hoca E, Çakır E, Ataoğlu HE. The effect of visfatin levels on blood pressure and cardiac risk factors in patients with acromegaly. İstanbul Med J. 2025; 26(4): 329-34

Received: 24.05.2025
Accepted: 26.10.2025
Publication Date: 12.11.2025

Adipocytokines exert autocrine, paracrine, and endocrine effects on the body (13,14). Changes in adipose tissue disrupt the regulation mechanisms of adipocytokines and predispose individuals to many metabolic disorders such as inflammation of adipose tissue, insulin resistance, chronic systemic inflammation, and endothelial dysfunction (14,15). Visfatin belongs to the group of adipocytokines, though its involvement in metabolic conditions remains debated. Visfatin, secreted predominantly from visceral adipose tissue, exerts proinflammatory effects and activates multiple molecular signaling pathways, thereby contributing to endothelial dysfunction-an important early mechanism in the pathogenesis of atherosclerosis (16). These effects are thought to have significant implications for the development of cardiovascular diseases. Many studies have reported that visfatin levels are also associated with insulin resistance, diabetes and metabolic syndrome (17,18). Furthermore, some studies have shown that visfatin levels in patients with acromegaly may be associated with metabolic disorders, independent of the type of treatment (19).

In this study, we investigated how visfatin levels impact blood pressure, cardiac functions, and other clinical indicators in individuals with acromegaly.

Methods

Study Participants and Laboratory Evaluation

The study commenced following approval from the Ethics Committee of University of Health Sciences Türkiye, Haseki Training and Research Hospital (approval number: 388, date: 22.06.2016). Twenty-eight patients who were being followed up in the Endocrinology Outpatient Clinic of University of Health Sciences Türkiye, Haseki Training and Research Hospital with the diagnosis of acromegaly were included in our study by signing informed consent forms. The control group comprised 27 patients, free of chronic disease history, who presented to our hospital and signed informed consent forms. Detailed echocardiographic findings of the patient and control groups were recorded in consultation with cardiologists who have at least 10 years of echocardiographic experience, and the 24-hour blood pressure holter results of all participants were monitored. Blood samples for fasting blood glucose, insulin, alanine aminotransferase, creatinine, C-reactive protein (CRP), IGF-1, and visfatin were taken after fasting for at least 12 hours. First, the samples were stored at optimal room temperature for 30 minutes; then centrifuged at 4000 rpm for 10 minutes, and kept at -40 °C (for visfatin analysis) until the analysis day. Visfatin levels were determined by enzyme-linked immunosorbent assay (ELISA) method using Sun Red brand, (antibody-coated 96-well plate human visfatin, Shanghai, Sunred Biological Technology Co., China) ELISA kit, and absorbance values were determined on ELx800 (Biomedical Technologies Inc., USA) microplate reading device (Bio-Tek Instruments, INC.). Duration of medication use for acromegaly was recorded.

Statistical Analysis

IBM SPSS Statistics (version 25) software was used to analyze the data obtained in this study. Descriptive statistics are given as mean ± standard deviation, minimum and maximum and median. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For variables exhibiting normal distribution, the Independent Sample t-test was applied, while the Mann-Whitney U test was used for variables not conforming to a normal distribution. Categorical variables were presented as numbers and percentages (%), and the chi-square test or Fisher's exact test was used for intergroup comparisons when the expected cell count was <5. Pearson or Spearman correlation analyses were utilized to ascertain relationships between variables. Statistical significance was set at $p<0.05$. Comparative analyses of the related groups were performed to evaluate the relationship between biochemical parameters, cardiovascular measurements, and clinical data. The results were presented in tables, and statistically significant differences were indicated.

Results

When the groups were evaluated in terms of age, the mean age of the control group was 48.4±14.8 years, and for acromegaly patients, it was 45.0±9.7 years. No significant difference was observed between the two groups ($p=0.305$). The female sex ratio was lower in the control group than in acromegaly patients ($p=0.010$). Fasting glucose and IGF-1 values were higher in acromegaly patients ($p=0.001$ and $p<0.001$, respectively). Body mass index was statistically significantly higher in acromegaly patients compared to the control group ($p=0.034$). Regarding other anthropometric measurements, there was no significant difference between the control group and acromegaly patients, Table 1.

No significant difference was observed in blood pressure measurements between the two groups (Table 2).

The visfatin level was 17.8±29.3 ng/mL in the whole group (acromegaly + control). The median, minimum, and maximum values of visfatin were 9.0, 5.4, and 191.1, respectively. There was no difference in visfatin values between genders in acromegaly patients ($p=0.105$), but visfatin level was lower in acromegaly patients compared to the control group ($p=0.015$) (Table 3), (Graphic 1).

In the cardiological evaluations of acromegaly patients, the mean left ventricular end-diastolic diameter (LVEDD) was statistically significantly higher than that of the control group ($p<0.001$). In addition, the incidence of left ventricular hypertrophy was higher in patients with acromegaly compared to the control group ($p=0.048$) (Table 4).

No significant correlation was found between visfatin and IGF-1 levels ($p=0.060$). There was a positive correlation between visfatin levels and left atrium diameter ($p=0.023$). There was no correlation between visfatin levels and other demographic findings or laboratory findings. There was a positive correlation between IGF-1 and CRP and ejection fraction, and a negative correlation between IGF-1 and left ventricular end-systolic diameter ($p=0.002$, $p=0.026$, $p=0.043$, respectively) (Table 5).

No correlation was observed between visfatin levels, IGF-1 levels, and 24-hour blood pressure parameters (Table 6).

Table 1. Comparison of demographic data, anthropometric measurements and laboratory parameters between patients with acromegaly and control group

		Acromegaly		Control		
		n	%	n	%	p
Gender	Female	21	75	11	40.7	**0.010**
	Male	7	25	16	59.3	
		Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	p
Age (years)		45±9.7		48.4±14.8		0.305
Disease duration (years)		8.7±6.1	0-25 (9)			
Sandostatin treatment duration (months)		23.0±29.2	0-84 (6)			
Somatuline treatment duration (months)		8.7±19.4	0-72 (0)			
Dostinex treatment duration (months)		21.3±24.3	0-78 (12)			
Height (cm)		163.6±8.5	148-185 (162)	167.7±11.0	150-186 (167)	0.131
Weight (kg)		80.4±12.4	56-100 (81)	79.2±13.3	50-100 (78)	0.729
BMI (kg/m^2)		29.8±4.3	23-37 (29)	27.5±5.7	19-43 (27.0)	0.094
Hip circumference (cm)		111.1±7.5	97-127 (110)	106.4±11.8	89-141 (104)	0.082
Waist circumference (cm)		99.7±10.8	82-117 (101.5)	97.8±13.5	74-133 (97)	0.574
Glucose (mg/dL)		118.1±35.3	77-216 (107.5)	96.4±11.6	76-130 (94)	**0.001**
Insulin (uIU/mL)		7.6±4.4	2.1-18.1 (6.4)	7.0±4.3	2.6-23.8 (6.41)	0.545
CRP (mg/L)		3.3±3.8	0.2-17.8 (2.1)	3.1±4.1	0.3-22.5 (2.1)	1.000
ALT (U/L)		23.1±24.8	8-144 (16)	24.9±20.3	7-113 (17)	0.425
Creatinine (mg/dL)		0.69±0.23	0.39-1.59 (0.65)	0.74±0.15	0.42-0.96 (0.71)	0.293
IGF-1 (ng/mL)		295.4±261.0	1.55-1142 (234)	118.5±45.4	35.6-215 (117)	**<0.001**
HOMA-IR		2.3±1.7	0.61-1.87 (1.88)	1.5±0.8	0.56-3.48 (1.39)	**0.034**

BMI: Body mass index, CRP: C-reactive protein, ALT: Alanine aminotransferase, IGF-1: Insulin-like growth factor 1, Min: Minimum, Max: Maximum, SD: Standard deviation, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2. Evaluation of blood pressures of acromegaly patients and control group

	Acromegaly		Control		
24-hour BP findings (mmHg)	Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	p
Maximum systolic BP	154.9±25.6	113-213 (159)	159.5±25.7	109-204 (161)	0.482
Maximum diastolic BP	111.9±30.3	55-191 (106)	108.9±23.3	67-169 (108)	0.656
Minimum systolic BP	88.8±10.8	71-118 (87)	89.2±11.4	65-118 (90)	0.875
Minimum diastolic BP	51.9±10.3	40-82 (50)	55.9±13.1	30-78 (58)	0.190
Mean systolic BP	117.2±13.1	94-145 (113)	121.4±11.8	96-151 (120)	0.184
Mean diastolic BP	75.3±11.1	55-100 (75)	76.8±8.6	56-97 (77)	0.542

BP: Bood pressure, Min: Minimum, Max: Maximum, SD: Standard deviation

Table 3. Comparison of visfatin levels between acromegaly patients and control group

	Acromegaly		Control		
Visfatin (ng/mL)	Mean ± SD, (n)	p	Mean ± SD, (n)		
Male	11.09±8.42, (21)	0.105	12.41±12.71, (11)		
Female	12.69±16.56, (7)		32.52±49.49, (16)		
	Mean ± SD, (n)	Min-max (median)	Mean ± SD, (n)	Min-max (median)	p
All patients	11.5±10.7	5.4-50.2 (7.75)	24.3±39.7	5.7-191.1 (9.5)	**0.015**

Min: Minimum, Max: Maximum, SD: Standard deviation

Tablo 4. Evaluation of echocardiographic findings in acromegaly patients and control group

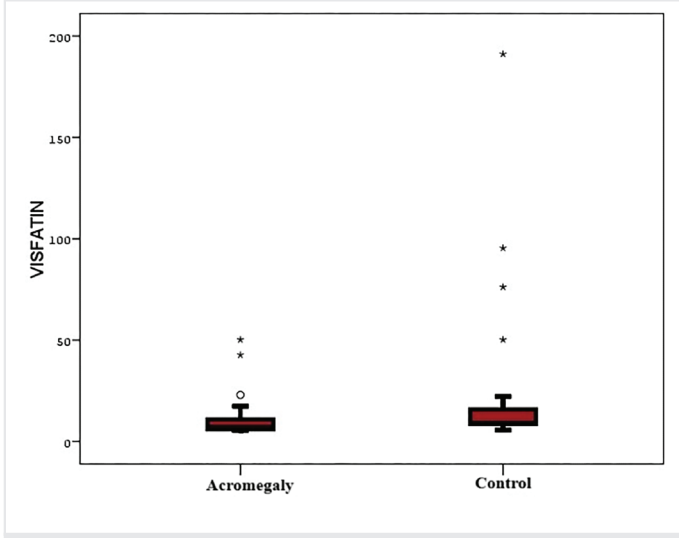
	Acromegaly		Control		
	Mean ± SD	Min-max (median)	Mean ± SD	Min-max (median)	p
Ejection fraction (%)	59.0±3.6	45-65 (60)	59.8±2.6	50-65 (60)	0.447
LVESD (mm)	38.5±5.4	27-50 (41)	36.5±7.5	24-50 (34)	0.197
LVEDD (mm)	51.0±3.4	45-60 (52)	45.3±7.4	30-52 (48)	**<0.001**
IVS thickness (mm)	11.5±0.9	9-13 (12)	11.1±1.1	9-13 (11)	0.169
PW thickness (mm)	11.1±0.9	8-12 (11)	10.8±1.0	8-12 (11)	0.173
	n	%	n	%	p
Left ventricular hypertrophy (+)	14	43.8	5	19.2	**0.048**

LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septum, PW: Posterior wall, Min: Minimum, Max: Maximum, SD: Standard deviation

Table 5. Association of visfatin and IGF-1 levels with other findings in patients with acromegaly

	Visfatin		IGF-1	
	rho	p	rho	p
IGF-1	-0.359	0.060		
Disease duration	-0.198	0.311	0.053	0.773
Sandostatin duration	-0.200	0.316	-0.025	0.895
Somatuline duration	-0.266	0.179	0.139	0.455
Dostinex duration	-0.332	0.091	0.104	0.577
Height	-0.335	0.082	0.104	0.571
Weight	-0.078	0.695	0.031	0.868
BMI	0.237	0.224	-0.128	0.486
Hip circumference	0.231	0.237	-0.112	0.542
Waist circumference	0.031	0.877	-0.102	0.578
Glucose	-0.021	0.914	0.278	0.124
Insulin	-0.099	0.623	0.341	0.061
CRP	0.069	0.727	-0.518	**0.002**
ALT	-0.117	0.570	0.004	0.984
Creatinine	-0.190	0.333	-0.128	0.484
Ejection fraction	0.330	0.086	-0.392	**0.026**
LVESD	-0.316	0.102	0.359	**0.043**
LVEDD	-0.241	0.217	0.337	0.059
IVS thickness	0.105	0.593	-0.247	0.173
PW thickness	0.004	0.983	-0.042	0.821
Left atrium diameter	0.427	**0.023**	-0.064	0.727
Right ventricle diameter	0.170	0.387	0.015	0.934

IGF-1: Insulin-like growth factor 1, BMI: Body mass index, CRP: C-reactive protein, ALT: Alanine aminotransferase, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, IVS: Interventricular septum, PW: Posterior wall



Graphic 1. Visfatin levels in acromegaly patients and control group

Table 6. Association of visfatin and IGF-1 levels with blood pressure values in patients with acromegaly

	Visfatin		IGF-1	
	rho	p	rho	p
Maximum systolic BP	0.321	0.110	-0.017	0.931
Maximum diastolic BP	0.352	0.078	-0.156	0.419
Minimum systolic BP	0.228	0.262	0.097	0.615
Minimum diastolic BP	0.059	0.777	0.192	0.319
Mean systolic BP	0.198	0.332	0.144	0.456
Mean diastolic BP	0.137	0.504	0.102	0.600

IGF-1: Insulin-like growth factor 1, BP: Bood pressure

Discussion

A limited number of studies in the existing literature suggest that serum visfatin levels might be linked to vascular inflammation, atherosclerosis, and increased vascular resistance. In our current investigation, we explored the relationship between visfatin levels and inflammatory markers, echocardiographic findings, and metabolic parameters.

Visfatin is an adipocytokine that is useful in demonstrating inflammation and endothelial damage. In a study conducted in Malaysia, circulating visfatin levels were found to be higher in metabolic syndrome, obesity and T2D (18). In a study conducted with acromegaly patients by Piskinpasa et al. (20), visfatin levels were associated with glycaemic dysregulation. Similarly, in the study conducted by Erten (21),

it was reported that visfatin levels may be predictive for metabolic risk. Conversely, Filippatos et al. (22) observed an increase in visfatin levels in patients with metabolic disorders compared to healthy controls. Some other studies, however, reported lower visfatin levels in patients with metabolic syndrome or obesity than in those without. The precise mechanism accounting for this variability in visfatin levels remains unclear (22).

Other studies found that visfatin levels were lower in patients with metabolic syndrome or obesity than in those without (23,24). However, the mechanism by which this variability in visfatin levels occurs has not yet been clearly elucidated.

In our study, visfatin levels were lower in patients with acromegaly compared with the control group. This may be because IGF-1 elevation leads to a decrease in the level of visfatin secreted from visceral adipose tissue by causing lipolysis in the long-term. The fact that the mean duration of acromegaly in the patients in our study was 8.7 years supports this long-term effect.

The cardiovascular effects of visfatin are multifaceted. A study by Lovren et al. (25) showed that visfatin had proangiogenic effects and was associated with increased endothelial nitric oxide synthesis, potentially conferring protective vascular effects. Conversely, Yu et al. (26) demonstrated that visfatin increased cardiac fibroblast proliferation and accelerated type 1 and type 3 collagen production in myocardial tissue, leading to myocardial fibrosis over time. This profibrotic effect may increase oxidative stress in cardiomyocytes and predispose cardiomyocytes to ischemic conditions and cardiac insufficiency.

Despite the known cardiovascular complications of acromegaly, including left ventricular hypertrophy (which was more prevalent in our patient group) and increased LVEDD, we found no statistically significant correlation between visfatin levels and most echocardiographic parameters. However, a notable positive correlation was observed between visfatin levels and left atrium diameter, suggesting a possible relationship between visfatin and atrial remodeling.

The lack of correlation between visfatin and most cardiovascular parameters may be explained by the fact that cardiovascular complications in acromegaly are primarily driven by direct GH/IGF-1 effects rather than adipocytokine-mediated mechanisms (1,4). Additionally, the cardiovascular side effects of visfatin occur mostly through inflammatory processes (15), and since our patients were predominantly treatment-controlled with suppressed disease activity, significant inflammation and associated cardiovascular changes may not have developed.

Our analysis of CRP levels as an inflammatory marker did not reveal a statistically significant relationship between CRP and visfatin levels in acromegaly patients. However, we found a negative correlation between IGF-1 and CRP levels, suggesting complex inflammatory regulation in this disease. Interestingly, there was no difference in CRP levels between acromegaly patients and controls, which may indicate that inflammatory processes were not prominently active in our treatment-controlled cohort.

Very few studies have evaluated the relationship between visfatin levels and metabolic parameters in patients with acromegaly. The prevalence of acromegaly varies between 40 and 70 per million. Therefore, there were only 28 patients with acromegaly in our hospital. This was the most significant limitation of our study. In addition, patients were receiving treatment for acromegaly, and most were under control. This may have prevented cardiovascular complications and possible metabolic changes from occurring. Our failure to find a clear relationship between visfatin levels and other parameters may be explained by these conditions. Therefore, studies with a larger number of patients, including untreated patients, and using follow-up data, may contribute to the literature.

Study Limitations

One main limitation was that there were only 28 patients with acromegaly in our hospital. In addition, since all patients were receiving treatment for acromegaly, cardiometabolic complications that typically develop secondary to acromegaly did not develop.

Conclusion

In such rare cases, evaluating the visfatin level with the predicted values may not be meaningful. More extensive studies are required to elucidate the significant effects of visfatin levels in more common diseases such as diabetes and hepatosteatosis. It would be more appropriate to perform such a study in treatment-naive patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of University of Health Sciences Türkiye, Haseki Training and Research Hospital (approval number: 388, date: 22.06.2016).

Informed Consent: All patients received information regarding the study's details and provided written informed consent.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 335-40
DOI: 10.4274/imj.galenos.2025.39924

Evaluation of the Impact of Preoperative Bowel Habits on the Success of Hemorrhoid Surgery: A Retrospective Observational Study of Grade III and IV Patients

İlyas Kudaş[1], Hüsna Tosun[2], Yahya Kemal Çalışkan[3], Olgun Erdem[2], Tolga Canbak[2], Aylin Acar[2], Fatih Başak[2]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of General Surgery, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, Clinic of General Surgery, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Kanuni Sultan Suleiman Training and Research Hospital, Clinic of General Surgery, İstanbul, Türkiye

ABSTRACT

Introduction: Hemorrhoidal disease is a common anorectal disorder that can significantly impair quality of life. While hemorrhoidectomy remains an effective treatment for advanced cases, individual factors such as gastrointestinal function may influence surgical success. This study aimed to quantify and evaluate the impact of preoperative bowel habits, particularly chronic constipation, on postoperative outcomes following hemorrhoid surgery in patients with advanced (grade III and IV) hemorrhoidal disease.

Methods: In this retrospective observational study, we analyzed 120 adult patients with grade III or IV hemorrhoids who underwent open or stapled hemorrhoidectomy between January 2020 and December 2024 at a single tertiary center. Preoperative bowel patterns were assessed using the Rome IV criteria, Bristol Stool Form Scale, and the Constipation Severity Instrument (CSI). Surgical success at six months was defined by the complete triple criteria complete wound healing, absence of significant pain [Visual Analog Scale (VAS) score of 2 or less], and no clinical recurrence of prolapse or bleeding. Postoperative outcomes, including complications, pain, healing duration, and recurrence, were compared between patients with and without preoperative chronic constipation.

Results: Chronic constipation was identified in 40.8% of patients. Surgical success was significantly lower in constipated patients (72.4%) compared to non-constipated individuals (91.7%, p=0.011). Constipation was also associated with longer healing times (mean 29.4±6.8 vs. mean 22.1±5.5 days, p<0.001), higher pain scores (VAS median: 4.0 vs. 2.0, p=0.004), and greater recurrence (at 6 months: 16.3% vs. 3.6%, p=0.018). Multivariate analysis confirmed chronic constipation [odds ratio (OR): 2.9] and CSI ≥20 (OR: 3.5) as independent predictors of surgical failure.

Conclusion: Preoperative constipation is a significant predictor of poorer 6-month outcomes following hemorrhoidectomy for advanced disease. These findings provide novel, quantifiable evidence supporting the need for systematic preoperative bowel assessment. Assessing and managing bowel habits preoperatively may enhance surgical success and reduce postoperative morbidity.

Keywords: Hemorrhoidal disease, constipation, bowel habits, surgical outcomes, hemorrhoidectomy, postoperative complications, Milligan-Morgan, stapled hemorrhoidopexy

Introduction

Hemorrhoidal disease is one of the most prevalent anorectal disorders worldwide, affecting approximately 4% of the adult population and representing a leading cause of outpatient colorectal consultations (1). It is characterized by symptomatic enlargement and distal displacement of the normal anal cushions, manifesting clinically with symptoms such as rectal bleeding, prolapse, itching, and discomfort (2). When conservative management fails, surgical intervention becomes necessary, particularly in cases classified as grade III or IV by the Goligher classification (3). Identifying patient-specific risk factors is essential for minimizing morbidity and optimizing patient selection for surgery.

Among the various surgical techniques, open hemorrhoidectomy (Milligan-Morgan procedure) and stapled hemorrhoidopexy (Longo technique) remain the most widely used methods due to their proven efficacy and long-term results (4). However, despite the technical success of these procedures, a considerable proportion of patients experience

Address for Correspondence: İlyas Kudaş MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of General Surgery, İstanbul, Türkiye
E-mail: ilyaskudas@hotmail.com **ORCID ID:** orcid.org/0000-0002-1319-9114

Cite this article as: Kudaş İ, Tosun H, Çalışkan YK, Erdem O, Canbak T, Acar A, et al. Evaluation of the impact of preoperative bowel habits on the success of hemorrhoid surgery: a retrospective observational study of grade III and IV patients. İstanbul Med J. 2025; 26(4): 335-40

Received: 22.07.2025
Accepted: 03.11.2025
Publication Date: 12.11.2025

suboptimal postoperative outcomes, including persistent pain, delayed healing, and recurrence (5). Such variability in outcomes has prompted a growing interest in identifying patient-specific factors that may influence the effectiveness of surgical treatment.

One such factor is gastrointestinal motility, including defecation patterns, particularly chronic constipation. Chronic constipation, defined by the Rome IV criteria, includes infrequent bowel movements, hard stools, straining, and a sensation of incomplete evacuation lasting for at least three months (6). It is a common complaint in the general population, with a reported prevalence ranging between 14% and 24% (7). The pathophysiology of constipation often involves colonic dysmotility, pelvic floor dysfunction, and defecatory disorders, all of which may adversely affect postoperative healing in anorectal surgery (8).

The link between constipation and hemorrhoidal disease is bidirectional. On the one hand, chronic straining and prolonged defecation are recognized risk factors for the development and progression of hemorrhoids. On the other hand patients undergoing surgery for hemorrhoidal disease may already have preexisting dysfunctional defecation patterns that complicate postoperative recovery (9). Furthermore, postoperative constipation can exacerbate pain, lead to surgical site trauma, and increase the likelihood of recurrence, making bowel regulation a critical aspect of patient management (10).

Several studies have highlighted the clinical implications of constipation in surgical populations. For example, Iyigun et al. (11) demonstrated that patients undergoing cardiac surgery with preoperative constipation were more likely to develop postoperative bowel dysfunction. In the context of colorectal and anorectal procedures, Bouchoucha et al. (12) emphasized the role of functional constipation as part of a broader colonic motility disorder that may impact surgical outcomes. However, specific quantitative data defining the relationship between preoperative chronic constipation, as diagnosed by established criteria, and postoperative outcomes in hemorrhoid surgery remain scarce and anecdotal.

Given this background, this study aims to address a critical research gap by systematically evaluating the impact of preoperative bowel habits-particularly the presence of chronic constipation-on the clinical success of hemorrhoidectomy. We hypothesize that patients with a history of constipation will experience poorer surgical outcomes, increased postoperative complications, and delayed recovery. Understanding this relationship cannot only help refine preoperative risk stratification but may also inform perioperative management strategies, including targeted bowel regulation protocols.

In this retrospective observational study, we assessed the defecatory habits of patients prior to undergoing hemorrhoid surgery using validated tools such as the Rome IV criteria, Bristol Stool Form Scale (BSFS), and the Constipation Severity Instrument (CSI). We then correlate these findings with postoperative outcomes over a six-month follow-up period, including rates of pain, wound healing, complications, and recurrence. Ultimately, the goal is to determine whether preoperative bowel dysfunction is a potentially modifiable risk factor that, if addressed appropriately, could lead to improved outcomes in hemorrhoid surgery.

Methods

Study Design and Setting

This study was designed as a retrospective, single-center, observational analysis conducted at the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Colorectal Surgery Unit of a tertiary care hospital. Patient records from January 2020 to December 2024 were retrospectively reviewed to evaluate individuals who underwent surgical intervention for hemorrhoidal disease. The study was approved by the Ethics Committee of Scientific Research, University of Health Sciences Türkiye, Ümraniye Training and Research Hospital (approval number: 219, date: 10.07.2025), and all data were anonymized in accordance with the principles outlined in the Declaration of Helsinki and national regulations related to data privacy. The study was designed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

Study Population

Adult patients aged 18 years or older who had undergone either open hemorrhoidectomy (Milligan-Morgan technique) or stapled hemorrhoidopexy (Longo technique) for grade III or grade IV hemorrhoidal disease were eligible for inclusion. The choice between open and stapled techniques was determined by the attending surgeon's preference and institutional guidelines. Only those with fully documented preoperative bowel habit data and complete postoperative follow-up information at six months were considered. Patients were excluded if they had a history of inflammatory bowel disease, colorectal cancer, prior major anorectal surgery, or constipation secondary to neurologic diseases such as Parkinson's disease or multiple sclerosis. Patients lacking postoperative follow-up data were also excluded to maintain outcome validity.

Sample Size and Data Collection

The sample size calculation was conducted to ensure adequate statistical power for the a priori defined primary outcome. Based on power analysis targeting a 95% confidence interval (CI) and 90% statistical power, with an assumed 15% difference in surgical success rates between constipated and non-constipated patients (80% vs. 95%) and a two-sided Chi-square test, the minimum required sample size was estimated at 115 patients. To account for potential data loss or exclusions, a total of 120 patients were ultimately included in the study. Due to the retrospective nature of the study, the power analysis was used to confirm that the available sample size was sufficient post hoc to detect the minimum hypothesized effect size (13). Data were extracted from the hospital's digital information system and verified through physical patient files where necessary. Figure 1 presents a flow diagram of the study, detailing patient selection, exclusion, and the number of participants assessed at each stage of the study.

Variables and Definitions

Collected variables included demographic information such as age, sex, and body mass index (BMI), as well as clinical characteristics including comorbid conditions and the Goligher grade of hemorrhoidal disease.

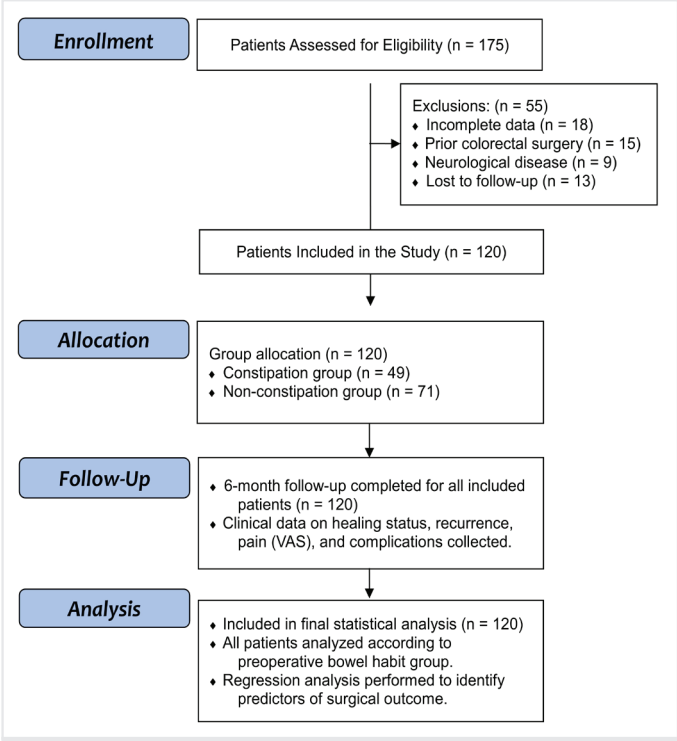

Figure 1. Flow diagram of patient selection and study inclusion (STROBE-style diagram)
VAS: Visual Analog Scale

Preoperative bowel function: Preoperative bowel function was evaluated using the Rome IV criteria for chronic constipation. According to these criteria, a diagnosis of constipation required the presence of at least two of the following symptoms for a duration of three months or more: straining during defecation, lumpy or hard stools, sensation of incomplete evacuation, anorectal obstruction, manual maneuvers to aid defecation, or fewer than three spontaneous bowel movements per week. Stool consistency was categorized using the BSFS, while the severity of constipation was quantified using the CSI, with scores of 20 or above considered to indicate moderate to severe constipation. The data for these validated instruments were extracted from structured patient questionnaires and physicians' notes completed as part of the standard preoperative consultation process.

Due to the retrospective nature of the study, the potential for recall bias or variability in documentation exist, and this is acknowledged as a limitation.

Primary Outcome: Surgical Success

Surgical success was strictly defined as the simultaneous presence of three criteria at the six-month follow-up visit:

1. **Complete wound healing:** Full epithelialization of the surgical site.
2. **Absence of significant pain:** Visual Analog Scale (VAS) score <3 of 2 or less.
3. **No clinical recurrence:** Absence of new prolapse, recurrent bleeding requiring intervention, or the presence of a symptomatic palpable anal mass.

Secondary outcomes: Secondary outcomes included pain scores (VAS), healing duration (in days, until full epithelialization), recurrence (at 6 months), and overall postoperative complications (Clavien-Dindo grade II or higher).

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0. Normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs), depending on the distribution. Categorical variables were summarized using frequencies and percentages. Comparative analyses between groups were performed using the independent samples t-test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables. To identify predictors of surgical failure, multivariate logistic regression was conducted, adjusting for age, BMI, type of surgery, Goligher grade, and constipation severity. In the multivariate model, "chronic constipation" (Rome IV diagnosis) and "CSI score ≥20" were included as distinct predictors to evaluate their independent associations with surgical failure. While these variables are related, they represent different aspects of constipation (diagnosis versus severity), and initial checks confirmed acceptable levels of collinearity for their simultaneous inclusion in the model. Statistical significance was established at a p-value of less than 0.05. The sample size calculation was performed using GPower 3.1.

Results

Patient Characteristics

A total of 120 patients met all inclusion criteria and were included in the final analysis. The mean age of the overall cohort was 44.6 years with a standard deviation of 12.7 years. Of these, 65 patients, accounting for 54.2% of the sample, were female. Preoperative constipation, as defined by the Rome IV criteria, was identified in 49 patients, corresponding to a prevalence of 40.8%. There were no statistically significant differences between the constipation and non-constipation groups in terms of age, sex distribution, BMI, or type of hemorrhoid surgery performed. Both open and stapled hemorrhoidectomy were evenly distributed between the groups, as shown in Table 1, which presents baseline demographic and clinical characteristics.

Surgical Success and Primary Outcome

Surgical success at six months was achieved in 96 patients, representing an overall success rate of 80%. However, when outcomes were stratified by preoperative bowel habits, a clear disparity emerged. In the constipation group, only 72.4% of patients achieved surgical success, compared to 91.7% in the non-constipation group. This difference was statistically significant, with a p-value of 0.011, indicating that preoperative constipation was associated with a lower likelihood of successful surgical outcomes.

Pain and Healing Duration

Pain severity, assessed using the VAS, was significantly higher in patients with constipation. The constipation group reported a median VAS score

Table 1. Patient demographics and preoperative characteristics

Variable	All patients (n=120)	Constipation (n=49)	No constipation (n=71)	p-value
Age (mean ± SD)	44.6±12.7	46.2±13.1	43.4±12.2	0.218
Female, n (%)	65 (54.2%)	30 (61.2%)	35 (49.3%)	0.176
BMI (kg/m²)	26.8±4.1	27.5±4.4	26.2±3.8	0.148
Goligher grade IV, n (%)	14 (11.7%)	7 (14.3%)	7 (9.9%)	0.345
Open hemorrhoidectomy	77 (64.2%)	31 (63.3%)	46 (64.8%)	0.864
Stapled hemorrhoidopexy	43 (35.8%)	18 (36.7%)	25 (35.2%)	

SD: Standard deviation, BMI: Body mass index

Table 2. Postoperative outcomes by constipation status

Outcome	Constipation (n=49)	No constipation (n=71)	p-value
Surgical success (%)	72.4%	91.7%	0.011
Pain score (VAS) median (IQR)	4.0 (2-7)	2.0 (1-4)	0.004
Healing time (days) (mean ± SD)	29.4±6.8	22.1±5.5	<0.001
Recurrence (at 6-months) (%)	16.3%	3.6%	0.018
Complication rate (Clavien-Dindo II or higher) (%)	22.4%	8.5%	0.031

SD: Standard deviation, VAS: Visual Analog Scale, IQR: Interquartile range

Table 3. Multivariate logistic regression analysis

Variable	OR (95% CI)	p-value
Chronic constipation	2.9 (1.4-6.1)	0.004
CSI score ≥20	3.5 (1.7-7.0)	0.001
Age ≥50	1.3 (0.6-2.8)	0.487
Open hemorrhoidectomy	1.1 (0.5-2.3)	0.782
Goligher grade IV	1.4 (0.4-4.9)	0.589

OR: Odds ratio, CI: Confidance interval, CSI: Constipation Severity Instrument

of 4.0 (IQR: 2-7), while patients without constipation had a median score of 2.0 (IQR: 1-4). The difference in pain perception was statistically significant (p=0.004), suggesting that postoperative constipation may contribute to increased discomfort during the recovery period. In terms of wound healing, patients with constipation required an average of 29.4±6.8 days for complete epithelialization, compared to 22.1±5.5 days in the non-constipation group. This prolonged recovery time was statistically significant (p<0.001) and may reflect the adverse effects of defecatory strain and delayed mucosal recovery.

Recurrence and Complications

Recurrence of hemorrhoidal symptoms, such as prolapse, bleeding, or the presence of new symptomatic disease, was more frequently observed in the constipation group. Six-month recurrence rates were 16.3% in constipated patients and 3.6% in those without constipation, a difference that was both clinically and statistically significant with a p-value of 0.018. Additionally, the overall rate of postoperative complications (Clavien-Dindo II or higher) was notably higher in the constipation group, with 22.4% of patients experiencing events such as infection, bleeding, or urinary retention. This was in contrast to an 8.5% complication rate in the non-constipation group (p=0.031), further emphasizing the negative impact of bowel dysfunction on postoperative outcomes. These findings are summarized in Table 2.

Predictors of Surgical Failure

Multivariate logistic regression analysis was performed to identify independent predictors of surgical failure. The presence of chronic constipation was associated with a nearly threefold increase in the odds of surgical failure, with an odds ratio of 2.9 and a 95% CI ranging from 1.4 to 6.1 (p=0.004). Additionally, patients with a CSI score of 20 or higher had a 3.5-fold increased risk of treatment failure (odds ratio: 3.5; 95% CI: 1.7-7.0; p=0.001). These results remained significant after adjusting for other factors such as age and type of surgery, as shown in Table 3. These data underscore the relevance of both the presence and severity of constipation as meaningful predictors of poor postoperative outcomes in hemorrhoidectomy patients.

Discussion

This retrospective observational study demonstrates a significant and independent association between preoperative bowel habits, particularly chronic constipation, and adverse postoperative outcomes following hemorrhoid surgery. Patients with constipation had lower surgical success rates, more complications, longer healing durations, and greater recurrence rates than those without constipation. These findings support our initial hypothesis and add to the growing body of evidence linking gastrointestinal motility with anorectal surgical outcomes.

Interpretation of Findings

Our results revealed that 40.8% of patients had preoperative constipation based on the Rome IV criteria, a prevalence that is higher than in the general population and may reflect the known association between constipation and hemorrhoidal disease progression (1). Within this subgroup, the rate of surgical success was significantly lower (72.4%) compared to patients without constipation (91.7%), underscoring the potential role of bowel dysfunction in surgical recovery. The observed differences in healing time and postoperative pain may be attributable

to increased intrarectal pressure during defecation, mechanical stress on the surgical wound, impaired local perfusion, and mucosal trauma associated with hard stools and straining (6,7).

Constipation severity, as assessed by the CSI, was also independently associated with poor outcomes. This suggests that symptom intensity, not just the presence of constipation, may affect surgical prognosis. Our multivariate regression identified both chronic constipation and CSI score ≥20 as significant, independent predictors of surgical failure, emphasizing the need for nuanced preoperative assessment.

Comparison with Previous Studies

While constipation's impact on abdominal and cardiac surgery has been explored (11), limited studies have specifically addressed hemorrhoidectomy outcomes. Iyigun et al. (11) demonstrated a link between preoperative constipation and postoperative dysfunction in cardiac surgery patients, and Bouchoucha et al. (12) described constipation as part of a broader spectrum of colonic dysmotility contributing to anorectal dysfunction. The lack of detailed, quantitative evidence for hemorrhoid surgery meant that preoperative bowel management was largely based on expert opinion (10). Our study is one of the first to quantify and statistically validate the role of preoperative constipation in predicting hemorrhoid surgery outcomes using validated scoring systems.

Clinical Context and Etiology

The management of hemorrhoidal disease requires a deep understanding of its basic pathophysiology, which involves the deterioration of supporting connective tissue in the anal cushions, leading to displacement and symptomatic enlargement (14). While mechanical factors such as chronic straining, prolonged sitting, and hard stools are central to the development and progression of hemorrhoids, the clinical presentation often varies widely, ranging from intermittent bleeding to chronic prolapse (15). For grade III and IV hemorrhoids, surgical intervention is typically indicated and aims to eliminate prolapse and bleeding while minimizing postoperative morbidity (15). Given this complex etiology, the long-term success of surgery is highly dependent not only on the technical execution but also on the effective management of these underlying predisposing factors, chief among them dysfunctional bowel habits (14). Therefore, identifying patients with preoperative chronic constipation who are at higher risk for failure is a crucial step in optimizing surgical outcomes.

Clinical Implications

These findings highlight the importance of systematic evaluation of bowel habits prior to hemorrhoid surgery. Incorporating screening tools such as the Rome IV questionnaire, BSFS, and CSI in preoperative assessment could help stratify patient risk and guide targeted interventions. For high-risk patients (Rome IV positive and/or CSI ≥20), prophylactic bowel regulation strategies, including dietary modifications, laxatives, or pelvic floor therapy, should be initiated preoperatively.

Additionally, recognizing constipation as a modifiable risk factor offers an opportunity to refine surgical planning. For instance, patients with severe constipation may benefit from conservative treatment prior to surgery or alternative approaches that reduce postoperative straining.

Study Limitations

Despite its strengths, this study has inherent limitations due to its retrospective design. Its retrospective design may introduce selection bias, and reliance on documented patient-reported symptoms could lead to misclassification. Specifically, the retrospective application of the Rome IV criteria, BSFS, and CSI is a notable limitation, as these instruments are ideally administered prospectively to ensure complete and accurate patient recall of bowel habits. The single-center nature of the study limits generalizability. Moreover, follow-up was limited to six months, which may underestimate long-term recurrence. Finally, while we confirmed all surgeries were performed by experienced colorectal surgeons following standardized protocols, individual variations in surgical technique and surgical teams may still exist. Future prospective, multicenter studies with standardized bowel management protocols are needed to confirm these findings and establish evidence-based guidelines for perioperative bowel care in hemorrhoid surgery.

Conclusion

This study confirms that chronic constipation is a significant and independent predictor of poorer surgical outcomes following hemorrhoidectomy. Patients with constipation experienced more pain, longer healing periods, and a higher risk of recurrence and complications. Importantly, both the presence and severity of constipation, as assessed by standardized tools, were associated with these adverse outcomes.

Systematic evaluation of bowel habits before surgery should become a routine part of preoperative assessment for patients undergoing hemorrhoidectomy. By identifying and addressing constipation in advance, clinicians may improve the likelihood of successful recovery and reduce the burden of postoperative morbidity. These findings support a more integrated approach to patient care-one that combines surgical intervention with gastrointestinal functional optimization to enhance treatment outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Scientific Research, Ümraniye Training and Research Hospital (approval number: 219, date: 10.07.2025).

Informed Consent: Retrospective study.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 341-7
DOI: 10.4274/imj.galenos.2025.91033

Does Wearing a Real-Time Continuous Glucose Monitor (RT-CGM) All the Time Matter? A Cross-Sectional Study of Use Intensity and Fear of Hypoglycemia

Mehmet Gökhan Gönenli[1], Fadime Buket Bayram Kuvvet[1], Selin Çakmak Demir[2], Görkem Ayaş[3], Ahmet Bahadır Ak[1], Hayri Kağan Gören[1], Oğuzhan Deyneli[2], Dilek Yazıcı[2]

[1]Koç University Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye
[2]Koç University Faculty of Medicine, Department of Endocrinology, İstanbul, Türkiye
[3]Koç University Graduate School of Health Sciences, İstanbul, Türkiye

ABSTRACT

Introduction: Fear of hypoglycemia (FOH) hinders optimal glycemic control in type 1 diabetes (T1D). Real-time continuous glucose monitoring (RT-CGM) can alleviate FOH; however, the minimum sensor wear time required is unclear.

Methods: In this single-center, cross-sectional study, we analyzed 43 adults with T1D who had used RT-CGM during the preceding 24 weeks. Participants were classified as continuous users (sensor active every week, n=26) or intermittent users (cumulative 4-12 weeks, n=17). FOH was measured with the validated Turkish hypoglycemia fear survey II. Group differences were examined with Student's t or χ^2 tests (α=0.05). Pearson correlations and multiple linear regression were used to explore FOH predictors.

Results: Mean HFS II scores (continuous vs. intermittent) were 17.7±13.1 vs. 14.5±6.7 for behavior, 19.0±13.7 vs. 20.4±14.4 for worry, and 36.7±22.1 vs. 34.9±18.6 for total (no statistically significant difference was observed between groups). Higher HFS total correlated with poorer self-reported treatment adherence (r: -0.32, p=0.04) and showed a non-significant inverse trend with longer diabetes duration (r: -0.27, p=0.08). Worry scores were higher in participants who reported recent symptomatic hyperglycemia (p=0.03). In the multivariable model, RT-CGM use intensity was not an independent predictor of FOH (β =-1.2, 95% confidence interval: -9.5 to 7.1; p=0.77).

Conclusion: Partial RT-CGM use (4-12 weeks over six months) produced FOH scores comparable to uninterrupted use, suggesting that continuous wear may not be necessary for short-term psychological benefit. FOH remained linked to treatment adherence, diabetes duration, and recent hyperglycemic events. Larger prospective studies with objective wear time data are warranted to define the threshold at which RT-CGM confers additional FOH reduction.

Keywords: Diabetes mellitus type 1, continuous glucose monitoring, hypoglycemia, fear

Introduction

Real-time continuous glucose monitoring (RT-CGM) is considered the most effective technological tool for reducing acute and chronic complications in type 1 diabetes (T1D) mellitus. Fear of hypoglycemia (FOH) affects 50-85 % of adults with T1D and represents a key psychological barrier to optimal glycemic control (1-3). To avoid hypoglycemic episodes, many people deliberately maintain higher glucose levels, driving their glycated hemoglobin (HbA1c) by 0.5-1.0 percentage points above target and lowering health-related quality of life by up to 25% (4,5). In large observational cohorts, individuals with high FOH scores show a 60% increase in deliberate hyperglycemia and a 2.3-fold rise in diabetic ketoacidosis (6-9).

RT-CGM supplies continuous glucose values, trend arrows, and customizable alarms that directly address FOH related concerns (10-13). Landmark trials such as DIAMOND, GOLD, and IMPACT demonstrated 38-55% fewer severe hypoglycemic events, an 8-15% increase in timeinrange, and a 15-30% reduction in FOH as measured by the hypoglycemia fear survey-II (HFS-II) (14-17). In DIAMOND, for example, RT-CGM lowered HbA1c by 0.6% while improving the HFS-II behavior and worry subscales by 23% and 28%, respectively (18,19).

Despite the growing evidence base, critical knowledge gaps remain regarding how much sensor wear is necessary to obtain psychological benefit. Most studies focus on uninterrupted use and overlook structured, intermittent protocols (20-22). The IN CONTROL study found

Address for Correspondence: Mehmet Gökhan Gönenli MD, Koç University Faculty of Medicine, Department of Internal Medicine, İstanbul, Türkiye
E-mail: mgonenli@ku.edu.tr **ORCID ID:** orcid.org/0000-0003-2925-7048

Cite this article as: Gönenli MG, Bayram Kuvvet FB, Çakmak Demir S, Ayaş G, Ak AB, Gören HK, et al. Does wearing a real-time continuous glucose monitor (RT-CGM) all the time matter? A cross-sectional study of use intensity and fear of hypoglycemia. İstanbul Med J. 2025; 26(4): 341-7

Received: 08.08.2025
Accepted: 03.11.2025
Publication Date: 12.11.2025

sustained FOH improvements only among participants who used their sensor more than 85% of the time (23), whereas a multicenter analysis showed a clear dose-response relationship between sensor wear and FOH reduction (17). In addition, the interaction between insulin-delivery modality and RT-CGM adherence is poorly characterized; pump users typically achieve 88-95% adherence compared with 65-78% in pen users, yet the impact on FOH is uncertain (24,25).

Evidence-based guidance on prescribing and implementing RT-CGM is therefore urgently needed. The HypoCOMPaSS trial suggested that combining RT-CGM with insulin pump therapy yields the greatest FOH benefit (26), but a recent systematic review highlighted heterogeneous responses across patient sub-groups (20). These conflicting findings underscore the need for patientcentered RT-CGM strategies.

The present cross-sectional study addresses this gap by comparing continuous versus intermittent RT-CGM useintensity and examining their associations with FOH in adults with T1D. By clarifying whether partial sensor use is sufficient to alleviate FOH -and how insulin-delivery method modifies this relationship- we aim to provide practical guidance for diabetes teams and identify priorities for future research.

Methods

Study Design and Setting

This was a singlecenter, cross-sectional study carried out in the adult endocrinology clinic of Koç University Hospital between October 2023 and June 2025. The protocol was approved by the Koç University Committee on Human Research (approval number: 2023.357.IRB2.074, date: 19.10.2023) and complied with the Declaration of Helsinki. All participants gave written informed consent.

Participants

Adults (≥18 years) with T1D diagnosed for at least one year were screened consecutively. Inclusion criteria were:

1. RT-CGM use at any time during the preceding 24 weeks.

2. Ability to read and complete questionnaires in Turkish.

We excluded pregnancy, end-stage renal disease, cognitive impairment, or major psychiatric disease. Forty-three patients met the criteria and were enrolled.

Participants were divided, using device logs and patient diaries, into

- Continuous users - sensor worn every week during the 24-week window (n=26) and
- Intermittent users - cumulative wear 4-12 weeks (n=17).

Measures

Primary Outcome-Fear of Hypoglycemia

FOH was measured with the Turkish HFS-II. The version used in this study contains 32 items- 15 in the behavior subscale and 17 in the worry sub-scale - because the original Turkish validation removed worry item 19 for cultural reasons (27). Each item is scored from 0 (never) to 4 (always), giving sub-scale ranges of 0-60 and 0-68 and a total score range of 0-128; higher scores reflect greater fear. There is no universally accepted cut-off for clinical FOH in the HFS-II-TR; therefore, scores were treated as continuous variables. In the validation study, internal consistency was excellent (Cronbach's α: 0.77 for behavior, 0.91 for worry, 0.90 for total).

Exposure - RT-CGM UseIntensity

Use-intensity was defined as above (continuous vs. intermittent).

Covariates

Age, sex, diabetes duration, body mass index (BMI), HbA1c, insulin-delivery method (pump vs. pen), private insurance status, self-rated treatment adherence (5-point Likert scale), number of symptomatic hypo- and hyperglycemia episodes in the past month, and prior structured hypoglycemia education were extracted from records or patient interviews.

Sample-Size and Power

A priori calculation (twosided α: 0.05, power: 0.80) showed that 64 participants (32 per group) were needed to detect a moderate effect (Cohen's d: 0.5) in HFS-II total scores. Because only 43 patients were recruited, the study is underpowered and may incur type II error.

Statistical Analysis

Analyses were performed with SPSS v26 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test assessed normality. Data are expressed as mean ± standard deviation or median (interquartile range) and n (%).

Comparisons: Independent-samples t tests (or Mann-Whitney U) compared continuous variables; χ^2 (or Fisher's exact) compared categorical variables.

Associations: Pearson correlation (or Spearman when non-normal) examined links between FOH scores and covariates.

Multivariable model: Multiple linear regression estimated the independent effect of RT-CGM use-intensity (reference = intermittent) on the HFS-II total score, adjusting for all covariates listed above. Multicollinearity was checked (varianceinflation factor <2).

Twotailed $p<0.05$ signified statistical significance. Missing data were ≤5% for all variables and were imputed by series mean (continuous) or mode (categorical).

Results

Participant Flow and Baseline Characteristics

Of the 63 adults screened, five were excluded (end-stage renal disease: 2, pregnancy: 2, major psychiatric disorder: 1), and 15 did not return a completed survey, leaving 43 participants for analysis (Figure 1). The mean age was 42.1±11.5 years, and 67% were women. Twenty-six individuals (60%) wore RT-CGM continuously throughout the 24-week window, whereas 17 (40%) used it intermittently for a cumulative 4-12 weeks. Insulin-pump therapy was more common in continuous users (50% vs. 18%), while pen therapy predominated in intermittent users (82%). Private insurance coverage also differed (23% vs. 59%, p=0.02). All other demographic and clinical variables were comparable between the groups (Table 1).

Fear of Hypoglycemia Due to the Intensity of RT-CGM Use-Intensity

Mean HFS-II-TR scores were: behavior 17.7±13.1 vs. 14.5±6.7 (p=0.37), worry 19.0±13.7 vs. 20.4±14.4 (p=0.75) and total 36.7±22.1 vs. 34.9±18.6 (p=0.79) for continuous and intermittent users, respectively (Figure 2).

Bivariate Correlations

HFS-behavior correlated with HFS-worry (r: 0.46, p=0.002) and HFS-total (r: 0.75, p<0.001). Higher HFS-total was modestly associated with poorer self-rated treatment adherence (r =-0.32, p=0.04) and showed a non-significant inverse trend with diabetes duration (r =-0.27, p=0.08). No correlation was observed for age, BMI, or HbA1c (Table 2).

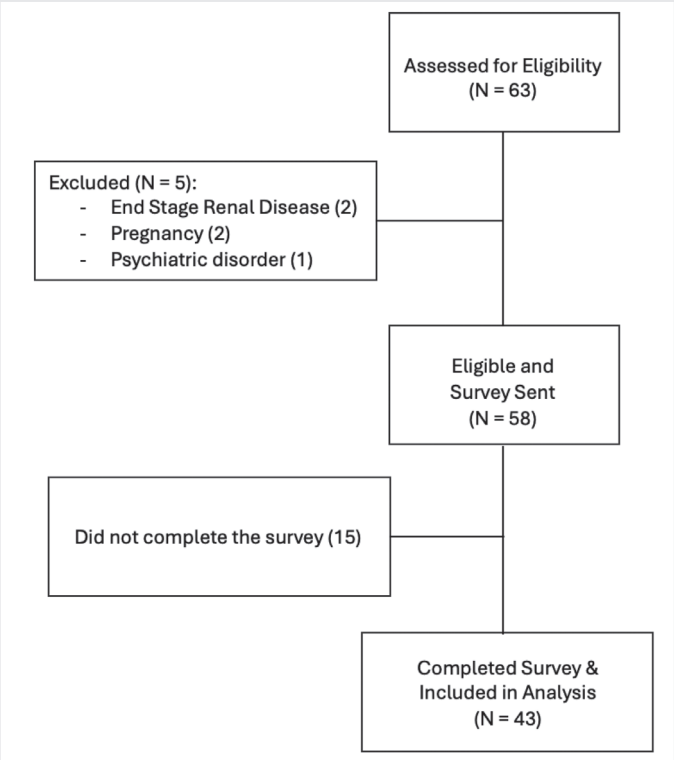

Figure 1. Participant flow chart for the cross-sectional RT-CGM study
Flow chart depicting the recruitment, exclusion, and retention of study participants. A total of 63 adults with type 1 diabetes were screened for eligibility. Five participants were excluded due to end-stage renal disease (n=2), pregnancy (n=2), and major psychiatric disorder (n=1). Of the 58 eligible individuals, 15 did not complete the survey. The final analytic sample comprised 43 participants who completed the fear of hypoglycemia survey and met all inclusion criteria

Sub-Group Comparisons

HFS-worry scores were higher among participants who reported structured hypoglycemia education (23.2±14.0 vs. 14.6±11.0, p=0.03) and those with at least one symptomatic hyperglycemia episode in the previous month (21.6±14.1 vs. 14.0±10.7, p=0.03). FOH did not differ by sex, educational level, smoking, alcohol use, or household composition (Table 3).

Multivariable Analysis

After adjustment for prespecified covariates, RT-CGM useintensity was not an independent predictor of HFS-total (β=-1.2 points, 95% confidence interval: -9.5 to 7.1, p=0.77). Only longer diabetes duration retained a modest negative association (β=-0.35 points year^{-1}, p=0.049). Model diagnostics were satisfactory (adjusted R^2: 0.19; variance inflation factor <1.6) (Table 4).

Discussion

This cross-sectional study assessed whether wearing RT-CGM sensors every week for six months confers greater psychological benefit than wearing them only part of the time. Contrary to our a-priori expectation, FOH scores did not differ between continuous and intermittent users, even though the continuoususe group contained a higher proportion of insulin-pump users. The finding challenges the common assumption of a strict dose-response relationship between sensor wear-time and psychological outcomes.

Our result diverges from landmark trials such as IN CONTROL and the dose-response analysis by Heinemann et al. (17), both of which reported larger FOH reductions when wear-time exceeded 85% (24). Important methodological differences may explain the discrepancy. Those studies enrolled participants with impaired hypoglycemia awareness and followed them for 12 months or longer, whereas our cohort comprised unselected clinic attenders followed for six months. An initial phase of structured RT-CGM exposure may be sufficient for many patients to internalize glucose-trend information and develop safer self-management behaviors. Beyond this point, additional sensor use might yield diminishing psychological benefits.

Table 1. Baseline demographic and clinical characteristics, overall and by RT-CGM use intensity

Variable	Continuous use (n=26)	Intermittent use (n=17)	Total (n=43)	p value†
*Female sex, n (%)	19 (73.1%)	10 (58.8%)	29 (67.4%)	0.32
Age, y, mean ± SD	44.7±12.3	38.1±9.1	42.1±11.5	0.06
Body mass index, kg m^{-2}, mean ± SD	24.1±3.6	23.8±3.7	24.0±3.6	0.82
*Private insurance, n (%)	6 (23.1%)	10 (58.8%)	16 (37.2%)	0.01
*Insulin pump therapy, n (%)	13 (50.0%)	3 (17.6%)	16 (37.2%)	0.03
Diabetes duration, y, mean ± SD	19.2±9.8	15.2±9.5	17.6±9.8	0.19
HbA1c, %, mean ± SD	7.4±0.9	7.1±1.0	7.3±0.9	0.29

*Percentages are column percentages. †Student's t-test for continuous variables; χ^2 test for categorical variables
SD: Standard deviation, HbA1c: Glycated hemoglobin, RT-CGM: Real-time continuous glucose monitoring

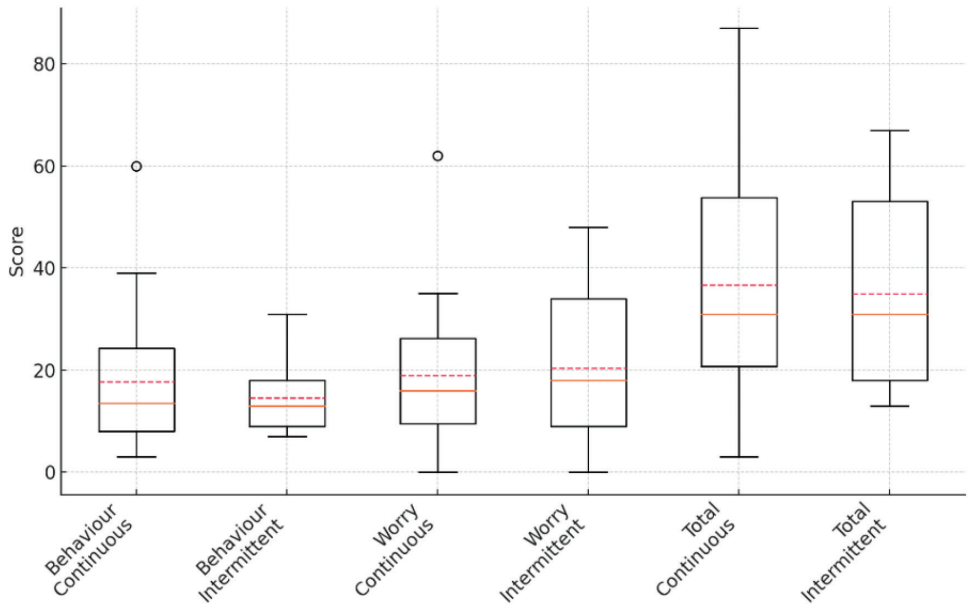

Figure 2. Fear of hypoglycemia scores by subscale and RT-CGM use-intensity
Box-and-whisker plots of hypoglycemia fear survey-II scores across subscales (behavior, worry, and total) compare real-time continuous glucose monitoring users (n=26) and intermittent users (n=17). The horizontal orange lines indicate the median, while red dashed lines represent the mean values. Boxes denote the interquartile range (IQR), and whiskers extend to 1.5× IQR. Outliers are plotted as individual dots. No statistically significant differences were observed between groups for any subscale (Student's t test; behavior p=0.37, worry p=0.75, total p=0.79)

Table 2. Pearson correlations between HFS-II scores and continuous covariates (n=43)

Covariate	HFS-behavior (r, p)	HFS-worry (r, p)	HFS-total (r, p)
Age (years)	0.08 (0.61)	0.04 (0.80)	0.06 (0.71)
Body mass index (kg m^{-2})	-0.05 (0.76)	-0.11 (0.48)	-0.09 (0.58)
HbA1c (%)	0.09 (0.55)	0.14 (0.37)	0.12 (0.43)
Diabetes duration (years)	-0.22 (0.16)	-0.28 (0.07)	-0.27 (0.08)
Treatmentadherence score†	-0.30 (0.05)	-0.28 (0.07)	-0.32 (0.04)
Symptomatic hypoglycemia (events · $month^{-1}$)	0.15 (0.34)	0.18 (0.25)	0.17 (0.28)
Symptomatic hyperglycemia (events · $month^{-1}$)	0.21 (0.18)	0.31 (0.03)	0.27 (0.09)

†Five-point Likert scale, 5: excellent adherence. HbA1c: Glycated hemoglobin, HFS: Hypoglycemia fear survey

Table 3. Group comparisons of HFS-II scores across selected categorical variables

Variable	Category	Behavior mean ± SD	p†	Worry mean ± SD	p†	Total mean ± SD	p†
Sex	Female (n=29)	17.9±12.0	0.21	21.4±14.1	0.20	39.3±20.5	0.12
	Male (n=14)	13.4±8.2		15.7±12.7		29.1±19.6	
Insulin-delivery modality	Pen (n=27)	17.6±11.3	0.35	18.5±11.7	0.51	36.1±19.3	0.95
	Pump (n=16)	14.4±10.5		21.4±17.1		35.8±23.3	
Structured hypoglycemia education	Yes (n=33)	16.5±11.8	0.89	21.3±15.1	**0.02**	37.8±22.2	0.17
	No (n=10)	16.0±8.4		13.9±5.8		29.9±13.0	
Symptomatic hyperglycemia (past month)	Present (n=32)	16.3±8.9	0.89	22.2±13.8	**0.03**	38.5±18.4	0.17
	Absent (n=11)	16.8±16.3		11.9±11.0		28.7±25.4	

†Independent-samples t-test. Bold p values indicate statistical significance at α: 0.05. SD: Standard deviation, HFS-II: Hypoglycemia fear survey-II

Table 4. Multiple linear regression predicting HFS-II total score (n=43)

Predictor (reference)	B ± SE*	95% CI	Standardized β	p
RT-CGM use intensity (continuous: 1, intermittent: 0)	-1.2±4.0	-9.5 to 7.1	-0.04	0.77
Diabetes duration (years)	-0.35±0.17	-0.70 to -0.01	-0.32	0.04
Age (years)	0.08±0.18	-0.29 to 0.45	0.07	0.66
Female sex (male: 0)	4.6±5.7	-6.9 to 16.1	0.13	0.44
HbA1c (%)	1.9±2.2	-2.6 to 6.4	0.14	0.39
Insulin pump therapy (pen: 0)	3.1±5.0	-7.1 to 13.3	0.10	0.54
Private insurance (no: 0)	5.8±5.3	-5.1 to 16.7	0.17	0.29
Treatment-adherence score†	-2.1±1.1	-4.4 to 0.2	-0.28	**0.06**
Symptomatic hypoglycemia (events · mo^{-1})	0.22±0.43	-0.66 to 1.10	0.09	0.62
Symptomatic hyperglycemia (events · mo^{-1})	0.58±0.36	-0.15 to 1.31	0.24	0.11

*B ± SE indicates the unstandardized regression coefficient (B) and its standard error (SE). †Five-point Likert scale; higher scores indicate better adherence. HFS-II: Hypoglycemia fear survey-II, RT-CGM: Real-time continuous glucose monitoring, HbA1c: Glycated hemoglobin, CI: Confidence interval
The Turkish version of the hypoglycemia fear survey-II consists of 32 items, divided into behavior (15 items) and worry (17 items) subscales. Each item is rated from 0 (never) to 4 (always), with higher scores indicating greater fear. Cronbach's α values are 0.77 (behavior), 0.91 (worry), and 0.90 (total) (27).

Several recent real-world investigations support this interpretation. A 2023 systematic review and meta-analysis including 51 studies (8,966 adults with T1D) showed that reductions in FOH (HFS-worry subscale) occurred after as little as eight weeks of real-time CGM use, indicating that psychological benefits can emerge early (28). Similarly, the FUTURE cohort study (1,905 adults using intermittently scanned CGM) reported significant improvements in HFS-worry scores over 24 months among individuals with impaired hypoglycemia awareness (22.8 → 20.6, p=0.002), although adherence criteria were not specified (29). Another prospective study of 121 adults with severe hypoglycemia found increased confidence in managing low glucose after 12 months of isCGM use, with participants describing a greater sense of safety even with intermittent scanning (30). Together with our data, these studies suggest that for many adults, a partialuse strategy may be psychologically adequate, especially when cost or device fatigue threatens long-term adherence.

The role of insulin-delivery modality warrants comment. As expected, pump therapy was more common among continuous users, mirroring registry data that show 88-95% RT-CGM adherence in pump users versus 65-78% in pen users (24,25). Nevertheless, insulin modality did not remain a significant predictor of FOH after multivariable adjustment. This finding contrasts with the randomized HypoCOMPaSS trial, where combining RT-CGM with pump therapy produced the largest FOH gains (26). Our observational design, shorter follow-up and inclusion of participants using next-generation pens may have diluted modality-specific effects.

Emerging data from automated insulin-delivery systems provide additional context. A 2024 real-world study of hybrid closed-loop therapy demonstrated 24.9% reductions in FOH despite average time in automatic mode of only 64.3% (31). Algorithms that attenuate both hypo- and hyperglycemic excursions may therefore magnify the psychological benefit of partial sensor use; some of our intermittent users may have experienced a similar effect through behavioral pattern recognition even without closed-loop automation.

Study Limitations

Key strengths include the use of a HFS-II-TR instrument, collection of objective wear-time logs, and adjustment for multiple clinical and socioeconomic confounders. Limitations, however, must temper interpretation. First, the sample was underpowered to detect small between-group differences; a priori calculation indicated that 64 participants would be required for 80% power. Recruitment was particularly challenging due to the limited accessibility and high cost of RT-CGM devices in our country, which restricted the eligible sample size. Second, our six-month window may be too short to observe incremental psychological advantages of continuous use. Third, sensor wear-time was classified categorically rather than as a continuous percentage; finer granularity might reveal threshold effects. Finally, FOH and treatment adherence relied on self-report and may be prone to recall or social-desirability bias.

Clinical Implications

For adult outpatients already familiar with RT-CGM, prescribing continuous wear may not be essential to achieve shortterm FOH relief. Structured intermittent protocols- particularly when combined with targeted hypoglycemia education- could represent a costeffective alternative, reserving full-time sensor use for those with persistent FOH or high hypoglycemic risk. Clinicians should therefore individualise wear-time targets, taking patient preference, insurance coverage, and technology fatigue into account.

Future Research

Prospective studies with larger samples and ≥12-month follow-up should validate the apparent plateau in FOH benefit beyond moderate wear-time and explore whether hybrid closed-loop systems shift this threshold. Mixed-methods designs incorporating qualitative interviews would help clarify which sensor features (alarms, trend arrows, retrospective reports) drive psychological improvement and for whom.

Conclusion

In this real-world cohort of adults with T1D, wearing an RT-CGM sensor for only 4-12 weeks over a six-month period yielded fearofhypoglycemia scores that were indistinguishable from those of users who wore the sensor continuously. FOH remained primarily associated with treatment adherence, diabetes duration, and recent glycemic excursions rather than with sensor wear-time or insulin-delivery modality. These findings suggest that structured intermittent RT-CGM protocols could meet short-term psychological needs in many patients, although larger prospective studies are required to confirm the wear-time threshold that confers additional benefit.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Koç University Committee on Human Research (approval number. 2023.357.IRB2.074, date: 19.10.2023).

Informed Consent: All patients received information regarding the study's details and provided written informed consent.

Footnotes

Authorship Contributions: Concept - M.G.G., F.B.B.K., S.Ç.D., O.D., D.Y.; Design - M.G.G., F.B.B.K., S.Ç.D., G.A., O.D., D.Y.; Data Collection or Processing - S.Ç.D., G.A., A.B.A., H.K.G., O.D.; Analysis or Interpretation - M.G.G., F.B.B.K., G.A., O.D., D.Y.; Literature Search - M.G.G., F.B.B.K., S.Ç.D., G.A.; Writing - M.G.G., F.B.B.K., O.D., D.Y.

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

Financial Disclosure: The authors declared that this study received no financial support.

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İstanbul Med J 2025; 26(4): 348-55
DOI: 10.4274/imj.galenos.2025.99217

The Relationship Between CRP/Albumin Ratio and In-Hospital Mortality in Intensive Care Patients: A Retrospective Observational Study

Gül Çakmak, Abdurrahman Tünay

University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye

ABSTRACT

Introduction: Accurate prognostic assessment in intensive care units (ICUs) is crucial for early risk stratification and efficient resource allocation. The C-reactive protein to albumin ratio (CAR) has recently gained attention as a composite biomarker that reflects both systemic inflammation and nutritional status. The present study sought to determine whether CAR measured at ICU admission could predict in-hospital mortality among critically ill adults and to establish its optimal discriminatory threshold.

Methods: This single-center retrospective cohort study included 1,846 adult patients (aged ≥18 years) who were admitted to the ICU between January 2023 and June 2025. At the point of admission, demographic, clinical, comorbidity, and laboratory data were thoroughly recorded. Mortality predictors were evaluated via logistic regression methods. The capacity of CAR for discrimination was determined using receiver operating characteristic analysis.

Results: Overall in-hospital mortality was 24.2% (n=446). Non-survivors were significantly older, with lower body weight and body mass index, and with higher rates of diabetes, chronic kidney disease, malignancy, heart failure, sepsis, infection, and acute kidney injury (AKI). The CAR at admission was markedly higher in non-survivors (5.5±5.3 vs. 1.5±2.6, $p<0.001$). In multivariable logistic analysis, independent factors associated with in-hospital mortality included age, polypharmacy, heart failure, infection, AKI, and CAR. The best threshold identified for CAR was 1.715, providing 76.9% sensitivity and 73.6% specificity, while its negative predictive value reached 90.9%.

Conclusion: Admission-time CAR measurement proved to be an effective indicator of in-hospital mortality among ICU patients. Its simplicity and cost-effectiveness underscore its utility as a prognostic instrument for early risk stratification in critical care.

Keywords: CRP/Albumin ratio, prognostic marker, in-hospital mortality, intensive care, critical illness

Introduction

The precise and timely prognostic evaluation of patients in critical condition represents a cornerstone of modern critical care medicine. Conducting an accurate prognostic assessment is essential not only for tailoring therapeutic strategies but also for ensuring rational allocation of intensive care unit (ICU) resources, prioritization of clinical interventions, support of ethical decision-making processes, and enhancement of cost-effectiveness analyses. Accurate prognostic evaluation allows for the timely identification of clinical priorities in critically ill patients, facilitating appropriate decisions regarding palliative care and contributing to the reduction of both mortality and morbidity.

The use of established clinical scoring models-such as APACHE II, SAPS II, SOFA, and qSOFA-has become a cornerstone of contemporary intensive care management (1,2). Nevertheless, these indices present notable shortcomings: they depend on multiple physiological and laboratory parameters, are prone to interobserver variation due to the subjectivity of certain measurements, and typically capture a patient's status at a single point in time. Furthermore, since these systems were initially designed for specific populations, their applicability to the wider ICU cohort remains limited. Consequently, there is a growing demand for prognostic indicators that are simpler, more objective, more rapidly obtainable, and feasible for everyday clinical implementation.

In recent years, easily measurable laboratory-based biomarkers have gained prominence for predicting outcomes in critically ill patients. Several indices derived from standard hematologic and biochemical parameters-such as the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, systemic immune-inflammation index, prognostic

Address for Correspondence: Gül Çakmak MD, University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye
E-mail: drgulcakmak@gmail.com **ORCID ID:** orcid.org/orcid.org/0000-0001-6900-0293

Cite this article as: Çakmak G, Tünay A. The relationship between CRP/albumin ratio and in-hospital mortality in intensive care patients: a retrospective observational study. İstanbul Med J. 2025; 26(4): 348-55

Received: 01.10.2025
Accepted: 03.11.2025
Publication Date: 12.11.2025

nutritional index, and hemoglobin-albumin-lymphocyte-platelet score-have been frequently studied (3-6). Among these, the ratio of C-reactive protein to albumin ratio (CAR) has drawn particular attention as it combines two physiologically distinct yet complementary indicators: C-reactive protein (CRP), which mirrors systemic inflammation, and albumin, which reflects nutritional and hepatic synthetic capacity (7). This integrated measure provides a broader representation of both inflammatory and nutritional status, often outperforming the predictive strength of each parameter alone.

Previous studies have linked elevated CAR levels with higher rates of mortality, postoperative complications, and reduced long-term survival across diverse conditions, including sepsis, acute renal injury, major surgical procedures, and other critical illnesses (7-15). However, systematic evaluation of CAR within ICUs remains limited.

ICUs are multidisciplinary settings in which critically ill patients are managed due to various conditions such as trauma, infection, systemic inflammation, and multiorgan failure. Prognostic assessment in this patient population requires a comprehensive approach that simultaneously accounts for the acute physiological stress response, underlying comorbidities, and the risk of complications. In this context, CAR, by integrating markers of inflammation and physiological reserve, could act as an effective indicator for anticipating early complications including sepsis, acute kidney injury (AKI), and ventilator-associated pneumonia.

The present study was designed to investigate whether the CAR obtained at the time of ICU admission could serve as a predictor of in-hospital mortality among critically ill adults. A secondary goal was to determine the most appropriate CAR threshold for mortality prediction, evaluate its discriminative capacity, and assess whether it functions independently of other prognostic indicators. Furthermore, the study aimed to explore associations between CAR and other clinical outcomes beyond mortality, with the ultimate objective of determining its potential as a practical and easily measurable marker to support early risk evaluation and guide therapeutic decision-making in intensive care practice.

Methods

This investigation was designed as a retrospective cohort analysis performed at a single tertiary-level ICU. The study cohort consisted of adult patients (aged 18 years or above) who were hospitalized between January 2023 and June 2025.

Eligibility criteria required participants to be 18 years or older, to have stayed in the ICU for a minimum of 24 hours, and to have available admission measurements of both CRP and albumin. Consecutive sampling was applied to all patients fulfilling these inclusion criteria. Individuals were excluded if they were under 18 years old, had chronic liver disorders such as hepatitis or cirrhosis that could alter albumin levels, experienced repeated ICU admissions (only the first stay was analyzed), lacked baseline laboratory or demographic data, or were transferred from another critical care facility.

All study data were retrospectively obtained from the hospital's electronic medical record system following approval by the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval no: 191; date: July 25, 2025). Demographic characteristics at ICU admission and accompanying comorbidities-including hypertension, diabetes mellitus, coronary artery disease, arrhythmia, heart failure, valvular heart disease, chronic obstructive pulmonary disease, stroke, chronic kidney disease, malignancy, hypothyroidism, and polypharmacy-were documented. In addition, clinical conditions such as sepsis, pneumonia, infection, and AKI were also recorded.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics software, version 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous data was evaluated with the Kolmogorov-Smirnov test. Variables showing a normal distribution were summarized as mean ± standard deviation, while variables with a non-normal distribution were presented as median values with interquartile range (minimum-maximum). Categorical variables were expressed as frequencies and percentages.

Group comparisons were performed using the Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for those that did not follow a normal distribution. Associations between categorical variables were examined using the chi-square test or Fisher's exact test, where appropriate.

Predictors of mortality were evaluated using univariate logistic regression analysis. Variables with a p-value <0.05 in the univariate analyses were subsequently included in the multivariate logistic regression model. For variable selection in the multivariate analysis, the forward likelihood ratio (forward LR) method was applied. Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

The predictive performance of CAR for mortality was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) and 95% CI calculated. The optimal cut-off value was determined using the Youden index. For this cut-off, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. A p-value <0.05 was considered statistically significant for all analyses.

Results

A total of 1846 patients were included in the analysis, with a median age of 65 years (range 14-102) and a mean of 63.2±17.5 years. Of these, 54.4% were male (n=1005). The median body mass index (BMI) was 26.0 (range 12.9-51.9), with a mean of 26.9±5.8 kg/m², and the median body weight was 75.0 kg (range 30.0-156.0). Polypharmacy was present in 25.4% of the cohort (n=469). Respiratory comorbidities included chronic obstructive pulmonary disease (6.9%) and pneumonia at admission (4.3%). Sepsis was diagnosed in 4.1% of patients, while overall infections other than pneumonia accounted for 14.8%. AKI occurred in 9.5% of cases. The median CAR at admission was 0.7 (range 0.0-27.0), with a mean of 2.7±3.9. During the study period, 11.4% (n=211) of patients required readmission to the ICU, and the median ICU length of stay was 2 days (range 1-243; mean 7.1±16.8 days). The overall in-hospital mortality rate was 24.2% (n=446) (Table 1).

Patients who did not survive were generally older, had lower body weight and BMI, and exhibited a higher burden of comorbidities and polypharmacy (all p<0.05). Conditions such as diabetes mellitus, chronic kidney disease, malignancy, heart failure, sepsis, infection, and AKI were significantly more prevalent among non-survivors, whereas coronary artery disease was less common in this group. Although ICU readmission rates were similar between groups, the ICU stay was notably longer and CAR levels were markedly higher in non-survivors compared with survivors (p<0.001) (Figure 1, Table 2).

In univariate analysis, older age, lower body weight and lower BMI, polypharmacy, and comorbidities such as coronary artery disease, diabetes, chronic kidney disease, malignancy, heart failure, sepsis, infection, and AKI injury were all significantly associated with in-hospital mortality (p<0.05). In the multivariate model, age (OR: 1.012, p=0.003), polypharmacy (OR: 0.989, p<0.001), heart failure (OR: 0.995, p=0.024), infection (OR: 0.992, p<0.001), AKI (OR: 0.991, p<0.001), and CAR (OR: 1.403, p<0.001) remained independent predictors of mortality (Table 3).

ROC curve analysis demonstrated that CAR had a strong discriminative ability for predicting in-hospital mortality, with an AUC of 0.828 (95% CI: 0.806-0.851, p<0.001). The optimal cut-off value determined by the Youden index was 1.715, corresponding to an AUC of 0.753 (95% CI: 0.726-0.779, p<0.001). At this threshold, the sensitivity was 76.9%, the specificity was 73.6%, the PPV was 48.2%, and the NPV was 90.9%. These findings indicate that CAR ≤1.715 reliably identified survivors, whereas values >1.715 were strongly associated with mortality risk (Figure 2, Table 4).

Discussion

In this study, we found that the CAR assessed upon admission to the ICU was a significant and independent determinant of in-hospital mortality.

Table 1. Baseline characteristics of the study population

		Min-max			Median	Mean ± SD/n-%		
Age (years)		14.0	-	102.0	65.0	63.2±17.5		
Gender	Male					1005		54.4%
	Female					841		45.6%
Height (cm)		110.0	-	193.0	167.0	166.8±8.9		
Weight (kg)		30.0	-	156.0	75.0	74.9±16.5		
BMI (kg/m^2)		12.9	-	51.9	26.0	26.9±5.8		
Polypharmacy						469		25.4%
Comorbidity								
HT						939		50.9%
CAD						189		10.2%
DM						293		15.9%
CKD						137		7.4%
Arrhythmia						68		3.7%
Stroke						29		1.6%
Malignancy						302		16.4%
Hypothyroidism						128		6.9%
COPD						130		7.0%
HF						167		9.0%
VHD						103		5.6%
Sepsis						80		4.3%
Pneumonia						25		1.4%
Infection						274		14.8%
AKI						175		9.5%
CAR		0.0	-	27.0	0.7	2.7±3.9		
ICU readmission						211		11.4%
LOS (days)		1.0	-	243.0	2.0	7.1±16.8		
Mortality						446		24.2%

Continuous variables are presented as mean ± standard deviation for normally distributed data or median (minimum-maximum) for non-normally distributed data. Categorical variables are expressed as counts (n) and percentages (%)
Min: Minimum, Max: Maximum, SD: Standard deviation; n: Number of patients. HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, VHD: Valvular heart disease, AKI: Acute kidney injury, CAR: C-reactive protein to albumin ratio, LOS: Length of stay, ICU: Intensive care unit

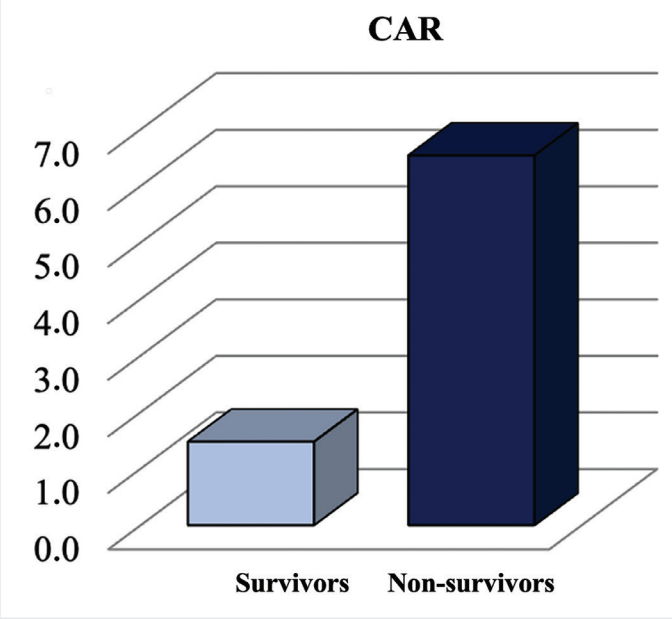

Figure 1. Distribution of C-reactive protein to albumin ratio in survivors and non-survivors
CAR: C-reactive protein to albumin ratio

This finding underscores the clinical importance of CAR as a practical prognostic tool in critically ill patients. Individuals who did not survive were generally older, exhibited lower body weight and BMI, and had multiple comorbidities alongside extensive medication use. Conditions such as diabetes, renal dysfunction, malignancy, heart failure, sepsis, and AKI were more frequent among non-survivors, whereas coronary artery disease occurred less often in this group. Moreover, CAR levels were markedly elevated in patients who died and correlated with longer ICU stays. Multivariate logistic regression further identified age, polypharmacy, heart failure, infection, AKI, and CAR as independent predictors of mortality risk.

As a prognostic indicator, the CAR captures the balance between systemic inflammatory activity and the patient's nutritional and physiological reserves. CRP reflects the dynamic and rapid response of the acute-phase reaction, serving as a marker of inflammatory status, whereas serum albumin, a negative acute-phase reactant, reflects nutritional reserves, hepatic synthetic function, and overall physiologic capacity (7). CAR, as a composite index, reflects both inflammatory activity and impaired physiologic reserve, granting it considerable prognostic value in identifying patients at risk for organ dysfunction, infection-related complications, and suboptimal recovery. In our study, the combination of lower body weight and BMI, a higher comorbidity load, polypharmacy, and the increased incidence of infection and AKI in the non-survivor group provide strong support for the underlying pathophysiological framework reflected by CAR. This conceptual framework reflects the notion that integrated biomarker indices, capturing both systemic inflammation and nutritional/physiologic reserve, demonstrate superior prognostic accuracy compared to isolated markers, as has been consistently documented in critical care.

To better delineate the clinical implications of our results, it is essential to compare them with previously published reports. In comparison with the study by Abdou et al. (16) conducted in septic patients, both investigations consistently demonstrated that older age and multiple comorbidities are strongly associated with mortality. the organ support requirements attributable to heart failure and polypharmacy emerge as recurrent factors associated with adverse outcomes. A striking contribution of our study is the remarkably high NPV (90.9%), which indicates that patients with lower CAR values have a substantially greater likelihood of survival, thereby providing practical utility for the early identification of low-risk patients. Similarly, Liu and Lv (9), in their study of patients with AKI, reported that CAR outperformed CRP or albumin alone in predicting 365-day mortality and remained an independent predictor in multivariate analysis. The fact that CAR values were significantly higher in non-survivors, and that these elevated levels were associated with long-term mortality in Cox regression, correspond well with our results. Across both studies, the consistent association of advanced age, heart failure, and AKI with mortality further reinforces the high-risk patient profile reflected by CAR.

The predictive significance of the CAR has likewise been highlighted in patients requiring postoperative intensive care. Oh, and colleagues (11) reported that CAR measured at the time of ICU admission served as an independent determinant of both short-term (30-day) and longer-term (1-year) mortality. Their analysis identified threshold values of 1.75 and 1.58 for 30-day and 1-year mortality, respectively, with higher CAR levels corresponding to substantially poorer survival outcomes. The cut-off value identified in our study (1.715) is consistent with this range, demonstrating comparable prognostic sensitivity. Within this investigation, advanced age and malnutrition emerged as principal determinants of mortality, consistent with the profile of our non-survivor group. However, while ischemic heart disease remained a significant risk factor for mortality in their study, our analysis paradoxically revealed a lower prevalence of coronary artery disease among non-survivors. Such a discrepancy may arise from selection biases inherent in specific intensive care populations, or reflect differing pathophysiological roles of cardiovascular comorbidities under variable patient characteristics. Notably, a study conducted in 2024 on a sepsis population also reported that coronary artery disease alone did not increase sepsis-related in-hospital mortality, a finding that lends support to the paradoxical observation in our cohort (17).

A retrospective analysis conducted by Oh et al. (18), demonstrated that an elevated CAR was shown to be an independent determinant of 30-day mortality among patients admitted to the ICU. However, the prognostic strength of CAR in that study was reported to be inferior to established scoring systems such as APACHE II, the Charlson Comorbidity index, and serum albumin levels. In our cohort, CAR maintained its role as an independent determinant of mortality in multivariate analysis, with prognostic power exceeding that of both age and heart failure. In particular, an OR of 1.403 with a narrow CI highlights that CAR may serve as a more robust predictor of mortality than age and comorbidities. This finding enhances the clinical applicability of CAR and suggests its potential use as a simple, complementary tool to complex scoring systems.

Ranzani et al. (8) provided valuable insights into the prognostic relevance of CAR in septic ICU patients by examining its association with mortality at both admission and discharge.

Table 2. Comparison of baseline demographic and clinical characteristics between survivors and non-survivors

		Survivors (n=1400)			Non-survivors (n=446)			p
		Mean ± SD/n-%		Median	Mean ± SD/n-%		Median	
Age (years)		62.2±17.7		65.0	66.6±16.4		68.0	**0.000**
Gender	Male	755	53.9%		250	56.1%		0.433
	Female	645	46.1%		196	43.9%		
Height (cm)		166.8±9.1		166.0	166.8±8.6		167.0	0.923
Weight (kg)		75.6±16.4		75.0	72.5±16.7		72.0	**0.000**
BMI (kg/m^2)		27.2±5.7		26.2	26.1±6.1		25.3	**0.000**
Polypharmacy		277	19.8%		192	43.0%		**0.000**
Comorbidity								
HT		714	51.0%		225	50.4%		0.839
CAD		155	11.1%		34	7.6%		**0.036**
DM		199	14.2%		94	21.1%		**0.001**
CKD		88	6.3%		49	11.0%		**0.001**
Arrhythmia		56	4.0%		12	2.7%		0.201
Stroke		19	1.4%		10	2.2%		0.191
Malignancy		193	13.8%		109	24.4%		**0.000**
Hypothyroidism		103	7.4%		25	5.6%		0.205
COPD		97	6.9%		33	7.4%		0.735
HF		110	7.9%		57	12.8%		**0.002**
VHD		81	5.8%		22	4.9%		0.494
Sepsis		38	2.7%		42	9.4%		**0.000**
Pneumonia		19	1.4%		6	1.3%		0.985
Infection		145	10.4%		129	28.9%		**0.000**
AKI		82	5.9%		93	20.9%		**0.000**
CAR		1.5±2.2		0.4	6.5±5.3		5.5	**0.000**
ICU readmission		159	11.4%		52	11.7%		0.861
LOS (days)		6.0±16.7		1.0	10.4±16.8		6.0	**0.000**

Continuous variables are presented as mean ± standard deviation and median (interquartile range), while categorical variables are expressed as number (n) and percentage (%). Comparisons between survivors and non-survivors were performed using the Student's t-test or Mann-Whitney U test for continuous variables, depending on distribution, and the chi-square (χ^2) test for categorical variables

Min: Minimum, Max: Maximum, SD: Standard deviation; n: Number of patients. HT: Hypertension, CAD: Coronary artery disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HF: Heart failure, VHD: Valvular heart disease, AKI: Acute kidney injury, CAR: C-reactive protein to albumin ratio, LOS: Length of stay, BMI: Body mass index

They reported that elevated CAR levels at either point were linked to higher mortality, with discharge measurements showing stronger predictive power, likely due to prolonged systemic inflammation. Similarly, our results align with these findings, demonstrating that admission-time CAR maintains significant prognostic value in critically ill patients, supporting its role as an early indicator of adverse clinical trajectories across different stages of critical illness.

Park et al. (19) reported CAR as an independent predictor of 28-day mortality in ICU patients, although with limited discriminatory capacity (AUC 0.594). Notably, our findings demonstrated superior prognostic performance for CAR, with an AUC of 0.828. These effects may be further compounded by differences in outcome definitions across studies: Park and colleagues assessed the prognostic role of CAR with respect to 28-day mortality, whereas our analysis examined its association with in-hospital mortality. Such variation in endpoints, together with the influence of fluid resuscitation and capillary leakage on albumin levels, may offer a potential explanation for the observed differences in prognostic performance (20).

CAR carries significant implications for clinical practice, particularly for early risk assessment, efficient ICU resource management, and as a complement to established severity indices. The easily derived measurement at ICU admission provides a practical indicator for early triage, corroborated by consistent reports identifying CAR as an independent predictor of mortality across varied ICU populations. Consistent with recent findings, calibration analyses of CAR-based models in sepsis populations have demonstrated excellent agreement between predicted and observed outcomes, highlighting their reliability and translational relevance in critical care (21).

Table 3. Univariate and multivariate logistic regression analyses of factors associated with in-hospital mortality

	Univariate analysis					Multivariate analysis				
	OR	95% CI			p	OR	95% CI			p
Age (years)	1.015	1.009	-	1.022	**0.000**	1.012	1.004	-	1.020	**0.003**
Weight (kg)	0.988	0.982	-	0.995	**0.001**					
BMI (kg/m^2)	0.967	0.948	-	0.986	**0.001**					
Polypharmacy	0.989	0.986	-	0.991	**0.000**	0.989	0.986	-	0.992	**0.000**
CAD	1.004	1.000	-	1.008	**0.038**	1.006	1.001	-	1.011	**0.013**
DM	0.995	0.992	-	0.998	**0.001**					
CKD	0.994	0.990	-	0.998	**0.001**					
Malignancy	0.993	0.990	-	0.996	**0.000**					
HF	0.994	0.991	-	0.998	**0.002**	0.995	0.991	-	0.999	**0.024**
Sepsis	0.987	0.982	-	0.991	**0.000**					
Infection	0.987	0.985	-	0.990	**0.000**	0.992	0.989	-	0.996	**0.000**
AKI	0.985	0.982	-	0.989	**0.000**	0.991	0.987	-	0.995	**0.000**
CAR	1.435	1.382	-	1.491	**0.000**	1.403	1.348	-	1.459	**0.000**
LOS (days)	1.014	1.007	-	1.020	**0.000**					

Variables with p<0.05 in univariate analysis were included in the multivariate model (forward LR method)
OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, CAD: Coronary artery disease, DM: Diabetes mellitus, CKD: Chronic kidney disease, HF: Heart failure, AKI: Acute kidney injury, CAR: C-reactive protein to albumin ratio, LOS: Length of stay, BMI: Body mass index

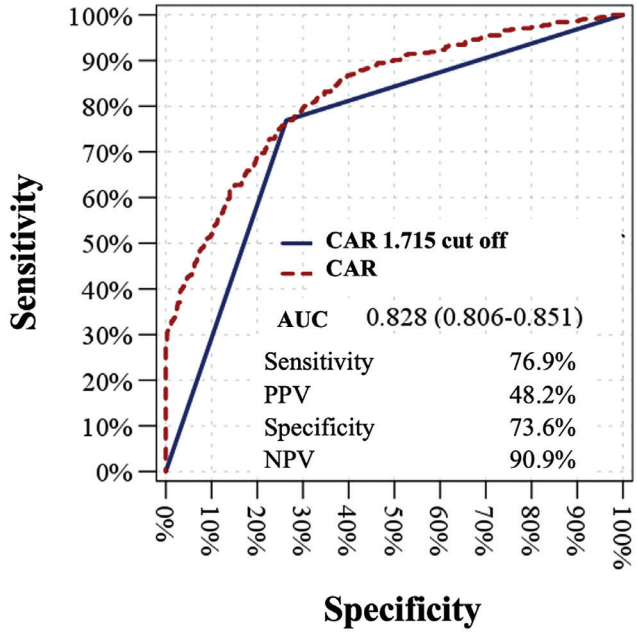

Figure 2. Receiver operating characteristic curve of the C-reactive protein to albumin ratio for predicting in-hospital mortality, with a cut-off value of 1.715
CAR: C-reactive protein to albumin ratio, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

In the context of ICU resource management, ensuring vigilant surveillance, timely implementation of comprehensive infection control measures, and strategies for nutritional optimization in patients with elevated CAR appear clinically warranted. Conversely, a low CAR, owing to its strong NPV, enables reliable identification of low-risk patients and supports more efficient allocation of resources. Consistent with this view, Siwach and Chintamani (22) underscored that the prognostic relevance of CAR extends beyond mortality prediction, as its integration into early risk stratification models may help guide appropriate allocation of ICU beds, monitoring intensity, and supportive interventions.

The prognostic role of CAR is most appropriately understood as complementary to established indices such as APACHE, PRISM, and the Charlson Comorbidity index, serving to refine and enhance their predictive accuracy. Notably, evidence from pediatric critical care populations has demonstrated that CAR discriminates mortality with high accuracy, performing comparably to PRISM-III, thereby reinforcing its role as an adjunctive tool across diverse age groups (23). The accumulating evidence positions CAR not merely as a prognostic marker but as a clinically actionable adjunct, capable of strengthening risk stratification and guiding efficient resource allocation beyond traditional severity scores. Such a role underscores its translational potential, highlighting that CAR may enhance both prognostic accuracy and operational decision-making across varied critical care contexts.

Study Limitations

The retrospective design of this study entails inherent limitations, including the limited capacity to adjust for unmeasured confounding factors, reliance on a single-center dataset, and the use of only admission-time CAR values. Future research should evaluate temporal changes in CAR dynamics and validate these findings through prospective, multicenter investigations.

Table 4. Diagnostic performance of the C-reactive protein to albumin ratio for predicting in-hospital mortality

		AUC		95% CI			p
CAR		0.828		0.806	-	0.851	**0.000**
CAR 1.715 cut-off		0.753		0.726	-	0.779	**0.000**
		Survivors	Non-survivors				%
CAR	≤1.715	1031	103	Sensitivity			76.9%
	>1.715	369	343	PPV			48.2%
				Specificity			73.6%
				NPV			90.9%

Values are presented as area under the receiver operating characteristic curve (AUC) with 95% confidence intervals (CI), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The optimal cut-off value was determined using the Youden index
CAR: C-reactive protein to albumin ratio

Conclusion

CAR measured at ICU admission emerged as an independent and robust indicator of in-hospital mortality. The identified cut-off value of 1.715 is clinically relevant, particularly due to its high NPV, which enables reliable early identification of low-risk patients. The simplicity, cost-effectiveness, and integrative capacity of CAR to combine both inflammation and physiological reserve into a single metric make it a valuable adjunct to traditional scoring systems. Taken together, the presence of sepsis, severe infections, and systemic inflammatory responses appears to amplify its predictive capacity, thereby reinforcing CAR's role as a simple yet powerful prognostic tool with direct applicability in critical care practice.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committeeof University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval no: 191, date: 25.06.2025).

Informed Consent: Retrospective study.

Footnotes

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

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

Financial Disclosure: The authors declared that this study received no financial support.

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Abdullah Soydan Mahmutoğlu
Abdurrahman Tünay
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Ahmet Zengin
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Arda Işık
Asım Enes Özbek
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