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Evaluation of The Quality and Reliability of Youtube Videos on Anterior and Posterior Ankle Impingement Syndrome

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ABSTRACT

Objective: YouTube is frequently used by patients and physicians for information. Ankle impingement syndrome (AIS) is a condition that affects both the anterior and posterior parts of the ankle joint. To the best of our knowledge, there is no study evaluating the quality of YouTube videos in AIS.

Materials and Methods: YouTube videos on anterior and posterior AIS were evaluated and compared by two European Foot and Ankle Society member orthopedic surgeons using the Journal of American Medical Association (JAMA), Quality Criteria for Consumer Health Information (DISCERN), and Global Quality Score (GQS). In addition, a new score, the AIS Specific Score, was used to evaluate the videos in this study.

Results: Fifty videos about anterior AIS and 43 videos about posterior AIS were evaluated. The mean duration of videos related to anterior AIS was 354.70 s (± 314.28) and the mean number of views was 27,166.08 ($\pm 54,898.69$). The mean duration of videos related to posterior AIS was 1594 s (± 424.94) and the mean number of views was 15,309.89 ($\pm 47,916.02$). When evaluating the quality of video content using scoring systems, videos related to anterior AIS have higher average JAMA, GQS, and DISCERN scores than those related to posterior AIS. However, this difference is only statistically significant for the DISCERN score ($p=0.045$).

Conclusion: The quality and reliability of YouTube videos on AIS are insufficient to meet the educational needs of patients or healthcare providers. These findings highlight the necessity for producing accurate, evidence-based educational videos and underscore the potential role of orthopedic societies and clinicians in creating standardized, high-quality online resources.

Keywords: Ankle impingement syndrome, Os trigonum, YouTube

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INTRODUCTION

The most reliable way to access accurate information in the field of health is of course to consult a doctor. However, the widespread and ease of use of the internet leads people to obtain information over the internet. One study found that 75% of participants had searched for health information online at least once in their lives.^[1] With the rise of social media, many patients now rely on online sources for health information, often even before consulting their doctor. Yet, it's important to realize that not all online health information is reliable or accurate, and trusting these sources can sometimes do more harm than good.^[2]

One of the important sources from which patients seek information is YouTube. With the growing interest in information presented in video format, content creators producing health-related information have also shifted their focus to this platform. The number of YouTube members, which has billions of users, continues to grow steadily.^[3]

Ankle impingement syndrome (AIS) is one of the major causes of ankle pain. It is characterized by pain that occurs with recurrent excessive dorsiflexion and plantar flexion. While it is often identified in athletes and dancers, this condition can also be observed in normal individuals.^[4] It can have either a soft tissue or bony origin.^[4] Different classifications are used to define the location of the impingement in the diagnosis of AIS. The most commonly used classifications are anterior AIS and posterior AIS.^[5]

There are numerous publications in the literature that evaluate the quality of YouTube video content, many of which are relevant to almost every area of orthopedics. Examples of these include rotator cuff tear,^[6] Bankart lesion,^[7] meniscus injury,^[8] anterior cruciate ligament injury,^[9] talus osteochondral lesions,^[10] and pes planus.^[11]

To the best of our knowledge, there has been no study evaluating the quality of YouTube videos related to AIS. The purpose of this study is to assess and compare the quality and adequacy of YouTube videos on anterior and posterior AIS. The hypothesis of this study was that the quality of YouTube videos would not be sufficient in anterior and posterior AIS.

MATERIALS AND METHODS

On January 14, 2024, using Google Chrome version 120.0.6099.71 (Official Build) (arm64), searched YouTube for the terms "anterior ankle impingement," "posterior ankle impingement," and "os trigonum" after clearing cache and cookies. Fifty-seven videos related to anterior ankle impingement and 51 videos related to posterior ankle impingement and os trigonum were evaluated from the three search results. Only videos with sufficient audio and video quality and in the English language were included in the study. Videos that have the same content, are not in English, or have poor audio and visual quality are excluded as criteria for the study. The study included 50 videos for the anterior ankle impingement group and 43 videos for the posterior ankle impingement group (Fig. 1).

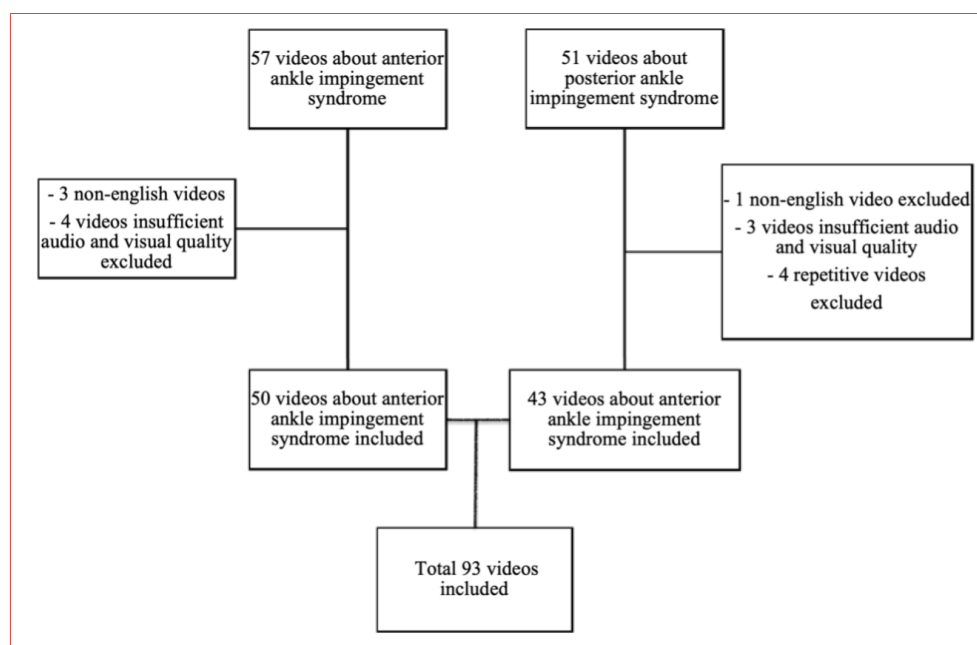


Figure 1. Flowchart of videos included in the study.

The names of the videos, their duration in seconds, the source that uploaded the videos, their content, the number of views, the time elapsed since they were uploaded, the number of likes and dislikes, the view rate (views/day), the likes rate ($\text{like} \times 100 / [\text{like} + \text{dislike}]$), and the video power index (VPI) ($\text{view rate} \times \text{like rate} / 100$) were evaluated. The sources uploading the videos were classified as doctors, physiotherapists, academics, medical sources, personal trainers, patients, and advertisers. The academic source included universities and research groups. Medical source was content uploaded by health websites. The video content was categorized into subgroups, including exercise videos, disease-specific information, patient experiences, surgical techniques, conservative treatment modalities, and advertising videos.

To ensure the objectivity of video content evaluations, the Journal of American Medical Association (JAMA), the Global Quality Score (GQS), Quality Criteria for Consumer Health Information (DISCERN), and the AIS Specific Score (AISSS) were utilized.

The JAMA score is a system for evaluating the accuracy and reliability of online sources. A total score of four indicates high reliability, while a score of zero indicates low reliability. This scoring system is frequently used as a tool for evaluating the reliability of online sources in the literature. Each criterion is awarded one point if met: (1) Authorship, (2) citation, (3) currency, and (4) explanation. A review of the literature shows that this scoring system is often used as a tool for evaluating the reliability of online sources^[6,12] (Table 1).

The GQS is a scoring system that rates the quality of content on a scale of 1–5^[13] (Table 1).

DISCERN score is a rating system developed by Charnock et al.^[14] It consists of 16 questions, each rated on a scale of 1–5. The score can range from a minimum of 16 to a maximum of 80. The videos were categorized based on their quality using the DISCERN scoring system. The categories include excellent quality (63–80 points), good quality (51–62 points), fair quality (39–50 points), poor quality (27–38 points), and very poor quality (16–26 points)^[6] (Table 2).

When evaluating the content of videos related to AIS, we found that there is no specific scoring system for this topic in the literature. Therefore, we used the AISSS, which we created in accordance with the guidelines established by the AAOS and accepted in the literature (Table 3). The criteria incorporated into the score – symptomatology, mechanism, diagnostic approach, conservative treatment elements, surgical indications, and post-operative considerations – were derived from AAOS educational materials and widely accepted literature on ankle impingement. In addition, relevant articles from the literature were considered while developing this score.^[10,15,16]

Table 1. JAMA criteria and global quality score
The JAMA Benchmark scoring (1 point per question)
1. Authorship (authorship, contributors, affiliations, and credentials)
2. Attribution (References and sources used for the content and all relevant copyright information noted)
3. Disclosures (ownership, sponsorship, advertising, commercial funding, and potential conflict of interests)
4. Currency (Dates that content was posted and updated should be indicated)
Global quality score
1. Poor quality, poor flow of the site, most information missing, not at all useful for patients
2. Generally poor quality and poor flow, some information listed but many important topics missing, of very limited use of patients
3. Moderate quality, suboptimal flow, some important information is adequately discussed but others poorly discussed, somewhat useful for patients
4. Good quality and generally good flow, most of relevant information is listed, but some topics not covered, useful for patients
5. Excellent quality and excellent flow, very useful for patients
JAMA: Journal of American Medical Association

The videos were evaluated once by two orthopedic surgeons who are members of European Foot and Ankle Society in a blind manner, and the scores given by the two surgeons were averaged when calculating the scores.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 27.0 (SPSS Inc., Chicago, IL, USA). Null hypotheses were rejected when $P < 0.05$. Interclass correlation coefficient (ICC) was used to evaluate interobserver agreement. The correlation of categorical variables with the number of views and quality scores was determined using analysis of variance. Categorical data were reported as frequencies and relative frequencies, while continuous data were reported as means. The Mann–Whitney U-test was used to compare non-normally distributed data after normality analysis.

RESULTS

In the detailed analysis of a total of 93 videos included in the study, the mean duration of videos related to anterior AIS was 354.70 s (± 314.28) and the mean number of views was 27,166.08 ($\pm 54,898.69$). The mean duration of videos related to posterior AIS was 1594 s (± 424.94) and the mean number of views was 15,309.89 ($\pm 47,916.02$). Posterior AIS videos are longer and have a higher like rate, whereas anterior AIS videos

Table 2. The 16 DISCERN questions, to be responded using a 1–5 (no to yes or low to high) score

1. Are the aims clear?
2. Does it achieve its aims?
3. Is it relevant?
4. Is it clear what sources of information were used to compile the publication?
5. Is it clear when the information used in the publication was used?
6. Is it balances and unbiased?
7. Does it provide details of additional sources of support and information?
8. Does it refer to areas of uncertainty?
9. Does it explain how the treatment works?
10. Does it explain the benefits of treatment?
11. Does it explain the risks of each treatment modality?
12. Does it explain what would happen unless treated?
13. Does it explain the effects of treatment on quality of life?
14. Is it clear that, more than one treatment choices exist?
15. Does it provide support for decision making?
16. Evaluate the overall quality of the publication as a source of information about treatment options based on answers to all questions above.

DISCERN: Quality Criteria for Consumer Health Information

have more views, and view rates but also show a higher dislike rate. Although high-quality videos were produced in both groups, the average scores of the groups are unfortunately very low. This indicates that the video content produced about AIS is neither reliable nor of high quality. The only statistically significant difference identified between AAIS and PAIS was in the DISCERN scores; however, here, the scores for AAIS were classified as “Poor,” while those for PAIS were classified as “Very Poor.” Thus, both groups are not of sufficient quality according to DISCERN. Other criteria evaluated are shown in Table 4.

The distribution of sources and video contents of the videos is shown in Table 5. When evaluating the sources uploading videos, it was observed that most videos related to posterior AIS came from academic (25.6%) and physician (30.2%) sources, this rate was academician (4%) and physician (30%) for anterior AIS.

A comparison of anterior and posterior AIS video scores is shown in Table 6. When evaluating the quality of video content using scoring systems, videos related to anterior AIS have higher average JAMA, GQS, and DISCERN scores than those related to posterior AIS. However, this difference is

Table 3. AISSS that we developed for the evaluation of content

AISSS

- Case presentation (2 Points)
 - Explains the symptomatology 1 point
 - Explains the symptoms associated with activities 1 point
- Information on ankle impingement (3 Points)
 - Explains the impingement syndrome 1 point
 - Defines the formation mechanism 1 point
 - Defines the most common locations in 1 point
- Diagnosis and evaluation (2 Point)
 - Mentions physical examination and findings 1 point
 - Mentions imaging methods 1 point
- Conservative treatment (3 Points)
 - Mentions activity modification and avoidance of provocative activities
 - Mentions resting and physiotherapy 1 point
 - Explains brace use 1 point
- Surgical treatment (8 Points)
 - Mentions surgical treatment indications 1 point
 - Mentions that various surgical techniques exist 1 point
 - Mentions that typical ankle impingement commonly heal with arthroscopic debridement could be successfully treated 1 point
 - Explains that, in patients who do not benefit from arthroscopic debridement or in patients with wide lesions, another procedure is needed 1 point
 - Explains the advantages of arthroscopic surgery and its minimal invasive feature 1 point
 - Explains the pre-operative preparation 1 point
 - Explains the surgical position 1 point
 - Gives information about the surgical approach 1 point
- Post-operative care and complications (2 Point)
 - Mentions surgical risks (infection, nerve injury, vascular injury, phlebitis, swelling or bleeding, complications associated with surgical tools, need for reoperation) (in the presence of 3 complications 1 extra point is added) mentions hospitalization time and, post-operative rehabilitation

AISSS: Ankle Impingement Syndrome Specific Score

only statistically significant for the DISCERN score ($p=0.045$). Looking at the average AISSS, it is higher in the posterior impingement group, but the difference is not statistically significant ($p=0.547$).

The average scores for academic and physician-sourced videos were as follows: JAMA 2.06 (± 0.79), GQS 2.6 (± 0.83), DISCERN

Table 4. Descriptive statistics

	Mean	Minimum	Maximum	Std. deviation
Anterior impingement <i>n</i> =50				
Duration (s)	354.70	31.00	1267.00	314.28
Views	27,166.08	22	315,562	54,898.70
Number of days after upload	1761.84	40	4523	1200.48
Like	325.80	0	5839	864.04
Dislike	10.16	0	105	19.38
Observer 1 JAMA	2.02	1	4	0.742
Observer 2 JAMA	2.08	1	4	0.752
Observer 1 GQS	2.58	1	4	0.906
Observer 2 GQS	2.82	1	5	1.04
Observer 1 AISSS	7.02	2	18	3.48
Observer 2 AISSS	6.42	1	16	3.72
Observer 1 DISCERN	29.82	16	75	15.44
Observer 2 DISCERN	31.10	16	71	14.77
View rate	17.70	.03	151.49	30.48
Like rate	92.60	.00	100	19.66
Video power index	17.11	.00	148.82	29.76
Posterior impingement <i>n</i> =43				
Duration (s)	481.35	57	1594	424.94
Views	15,309.86	56	315,362	47,916.02
Number of days after upload	1806.79	37	4497	1175.73
Like	200.63	0	5800	877.98
Dislike	4.14	0	105	16.125
Observer 1 JAMA	1.86	1	4	0.774
Observer 2 JAMA	1.84	1	4	0.721
Observer 1 GQS	2.30	1	4	0.741
Observer 2 GQS	2.53	1	5	0.935
Observer 1 AISSS	6.88	2	18	3.75
Observer 2 AISSS	7.09	2	18	4.01
Observer 1 DISCERN	23.28	16	75	13.13
Observer 2 DISCERN	25.77	17	79	13.02
View rate	9.01	0.07	147.43	23.05
Like rate	93.03	0.00	100	21.32
Video power index	8.80	0.00	144.81	22.70

AISSS: Ankle impingement syndrome specific score; GQS: Global quality score; JAMA: Journal of American Medical Association; DISCERN: Quality Criteria for Consumer Health Information.

26.3 (± 11.4), and AISSS 7.31 (± 3.7). For videos uploaded by other sources, the average scores were JAMA 1.8 (± 0.73), GQS 2.5 (± 0.95), DISCERN 24.7 (± 12.3), and AISSS 7.2 (± 1.54).

The interobserver agreement for AISS, GQS, JAMA, and DISCERN was 0.877 (95% CI 0.814–0.918), 0.829 (95% CI 0.743–0.887), 0.905 (95% CI 0.857–0.937), and 0.938 (95% CI 0.906–0.959), respectively.

Table 5. Evaluation of sources and video contents of the videos

	Anterior impingement n=50 (%)	Posterior impingement n=43 (%)
Sources of the videos		
Academic	2 (4)	11 (25.6)
Physician	15 (30)	13 (30.2)
Non-physician	12 (24)	1 (2.3)
Trainer	8 (16)	8 (18.6)
Medical source	12 (24)	4 (9.3)
Patient	0 (0)	2 (4.7)
Commercial	1 (2)	4 (9.3)
Video contents		
Exercise education	15 (30)	8 (18.6)
Disease specific knowledge	21 (42)	24 (55.8)
Surgical technique or approach	11 (22)	5 (11.6)
Non-surgical management	3 (6)	1 (2.3)
Advertising	0 (0)	3 (7)
Patient experience	0 (0)	2 (4.7)

DISCUSSION

The most significant finding of this study is that the quality and content of videos related to AIS are insufficient. In addition, this study is the first to evaluate the quality of YouTube videos related to AIS. In our study, we observed that the number of views, likes, view rates, and VPIs of videos related to anterior AIS were higher than those of videos related to posterior AIS. We believe that this is due to the higher frequency and awareness of anterior AIS compared to posterior AIS.

Internet usage is quite common among orthopedic doctors and patients. The frequency of use in communication, especially among young surgeons and patients, is increasing day by day.^[17,18] A study mentioned the possible relationship between patient satisfaction and a surgeon's use of social media platforms such as YouTube.^[19] Another study mentioned that YouTube is the most commonly used social media platform for surgical preparation education.^[20] Since YouTube is one of the most commonly used social media applications by patients and surgeons, it is important to consider the quality of uploaded video content as an important source of information for accurate guidance. However, when examining studies that evaluate the quality of orthopedic YouTube videos, numerous findings indicate that the video quality is

Table 6. Comparison of contents related to anterior and posterior impingement

	Mean rank	Sum of ranks	p
Views			
Anterior Impingement	50.46	2523	0.183
Posterior Impingement	42.98	1848	
Duration (sec)			
Anterior Impingement	44.02	2201	0.251
Posterior Impingement	50.47	2270	
Number of days after upload			
Anterior Impingement	46.44	2322	0.829
Posterior Impingement	47.65	2049	
Like			
Anterior Impingement	51.28	2564	0.099
Posterior Impingement	42.02	1807	
Dislike			
Anterior Impingement	54.00	2700	0.004
Posterior Impingement	38.86	1671	
View rate			
Anterior Impingement	50.18	2509.00	0.221
Posterior Impingement	43.30	1862.00	
Like rate			
Anterior Impingement	42.16	2108.00	0.049
Posterior Impingement	52.63	2263.00	
Video power index			
Anterior Impingement	50.56	2528.00	0.170
Posterior Impingement	42.86	1843.00	
JAMA			
Anterior Impingement	50.82	2541	0.121
Posterior Impingement	42.56	1830	
GQS			
Anterior Impingement	50.91	2545.50	0.125
Posterior Impingement	42.45	1825.50	
AISSS			
Anterior Impingement	45.44	2272.00	0.547
Posterior Impingement	48.81	2099.00	
DISCERN			
Anterior Impingement	52.19	2609.50	0.045
Posterior Impingement	40.97	1761.50	

AISSS: Ankle impingement syndrome specific score, GQS: Global quality score, JAMA: Journal of American Medical Association, DISCERN: Quality Criteria for Consumer Health Information

insufficient.^[21-25] Our findings are similar to the literature in that the quality of YouTube video content in AIS is insufficient.

Harnett et al.^[26] evaluated the quality of YouTube videos on ankle arthroplasty in their study and reported a JAMA score of 2.5 ± 0.7 , a GQS score of 3.2 ± 1.0 , and a DISCERN score of 49.2 ± 11.5 . Yuce et al.^[10] reported a JAMA score of 0.85 ± 1.05 , a GQS score of 1.42 ± 0.77 , and a DISCERN score of 11.51 ± 14.02 in their study on osteochondral lesions of the talus in the ankle. Our study shows that the average JAMA score of 1.95 indicates low content reliability. In addition, the average GQS, AISS, and DISCERN scores of 2.56, 6.94, and 27.71, respectively, indicate poor quality video content. Low-quality AIS videos can lead to patients not receiving sufficient information and being misdirected. This can lead to conflicts between patients and physicians, and to patients receiving information that is incomplete or inaccurate. We do not yet have sufficient information about the problems that this situation may cause.

The average view counts for AIS are 27,166 for anterior impingement and 15,309 for posterior impingement. When reviewing similar publications in the literature, the average number of views per video was found to be 100,149 for shoulder instability,^[12] 288,597.7 for meniscus videos,^[8] and 423,472 for disc herniation. The reason for the low number of views on videos related to AIS may be due to the fact that this condition is less well-known compared to other evaluated pathologies.

Videos related to posterior ankle impingement were longer in duration and demonstrated a higher like rate compared to anterior AIS content. This may reflect the relative unfamiliarity of posterior impingement among patients and clinicians, prompting content creators – particularly physicians and academic sources – to provide more detailed and explanatory videos. Longer and more comprehensive content may also contribute to viewer satisfaction, as indicated by the higher like rate, even though the overall quality scores of these videos remained low.

Videos on YouTube that offer high educational value may not always be as popular, which could result in lower view counts. This may mean that videos aimed at helping patients receive fewer views.^[27] The number of views can be increased by preparing more interesting and high quality YouTube videos. In addition, shorter and more focused videos are more effective at capturing and maintaining an audience's attention, leading to higher rates of completion compared to longer videos.^[28,29] Paying attention to these, especially in medical-sourced videos, can increase viewing rates and help patients and healthcare professionals reach the right source.

In a study, it was mentioned that the most important factor for the information obtained from YouTube videos is the source

of the video.^[30] In their study, Celik et al.^[6] stated that although the videos uploaded by physicians were of higher quality than those uploaded by other sources, even these videos were not of sufficient quality. It has also been mentioned in other studies that videos from physicians and academic sources are of higher quality than videos uploaded from other sources.^[6,29] In our study, the JAMA, GQS, DISCERN, and AISS scores of academic and physician-based videos were found to be higher than those of other sources. However, the quality of these videos was not found to be at the desired level. Low-quality videos may lead to misconceptions regarding diagnosis and treatment, potentially influencing patient expectations, creating misinformation-driven anxiety, and placing additional educational burden on clinicians.

This study has some limitations. It should be noted that YouTube dynamics have constantly changing and evolving algorithms. When selecting video content to include in the study, only videos from the search date were considered. However, it is possible for video sources to remove the videos they upload at any time, making it impossible to access them. Even with the same keywords, it may not be possible to obtain the same results in searches conducted on different days. Another limitation is the AISS scoring system we use. Although this scoring system was developed by the authors for this study with the aim of maximizing objectivity in evaluations, it can still be interpreted differently by different author. The other limitation of this study appears to be the use of specific keywords and the restriction to English-language videos. Patients may use different search terms, and video quality may vary across different languages. Another important limitation is the wide variation in upload dates. Older videos may not incorporate contemporary diagnostic or treatment concepts, potentially affecting quality scores and contributing to inconsistencies between videos.

CONCLUSION

Although anterior AIS videos had higher visibility metrics, both groups demonstrated similarly poor quality, with only a small but significant difference in DISCERN scores favoring anterior AIS. To ensure patients and doctors obtain accurate and useful information, there is a need for higher quality video content to be uploaded to YouTube.

DECLARATIONS

Ethics Committee Approval: This study does not involve human participants in a manner that requires ethical approval according to the Declaration of Helsinki; therefore, ethics committee approval was not required.

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Healthcare-Associated Infections and Antimicrobial Resistance Rates Developing in Intensive Care Units

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ABSTRACT

Objective: The aim of this study is to evaluate the incidence, infection types, distribution of causative microorganisms, and antimicrobial resistance (AMR) patterns of healthcare-associated infections (HAIs) developing in intensive care units (ICUs).

Materials and Methods: This retrospective and observational study was conducted between January 1, 2023, and January 1, 2025. HAI diagnoses were made according to Centers for Disease Control and Prevention and National Healthcare-Associated Infections Surveillance Network (USHIESA) criteria. Total number of patients, patient-days, invasive device-days, infection types, and resistance profiles of causative pathogens were analyzed. Infection rates were calculated based on 1000 patient-days and 1000 device-days.

Results: During the study period, 6,152 patients and 28,129 patient-days were monitored. The rate of HAIs was 0.40%, and the incidence density was found to be 0.88/1000 patient-days. Ninety-six percent of the cases were catheter-related urinary tract infections, and 4% were central venous catheter-related bloodstream infections while ventilator-associated pneumonia was not detected. Seventy-six percent of the isolates pathogens were Gram-negative, and 24% were Gram-positive bacteria. The most frequently isolated Gram-negative bacteria were *Myroides* spp. (47.36%), followed by *Acinetobacter baumannii* (26.31%), *Klebsiella pneumoniae* (21.05%), and *Pseudomonas aeruginosa* (5.26%). All Gram-positive agents were identified as *Enterococcus* spp. High levels of AMR were detected in the isolates.

Conclusion: Although the incidence of HAI in the ICU is below the national reference threshold, the prevalence of *Myroides* spp. and resistant Gram-negative pathogens is noteworthy. The findings highlight the need to maintain effective surveillance systems and strengthen strategies to combat AMR.

Keywords: Antimicrobial resistance, Device-associated infections, Healthcare-associated infections, Intensive care unit, *Myroides* spp

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INTRODUCTION

Although hospital admission is primarily for diagnostic and therapeutic purposes, it exposes patients to a significant risk of healthcare-associated infections (HAIs). HAIs are a leading cause of morbidity and mortality worldwide, creating serious clinical and economic problems for healthcare systems. According to the World Health Organization, approximately 7–15% of hospitalized patients develop at least one HAI.^[1,2] This rate is higher in healthcare systems with limited resources and is closely associated with infection control infrastructure deficiencies, insufficient trained personnel, substandard disinfection practices, and problems related to the use of personal protective equipment.^[1,3]

Intensive care units (ICUs) are among the highest-risk areas for HAIs. The prevalence of invasive procedures, immunosuppressed patient populations, and severe clinical cases facilitate the infection development which, in return, prolongs hospital stays, increases treatment costs, and negatively impacts clinical outcomes. Furthermore, HAIs are strongly associated with the development and spread of antimicrobial resistance (AMR).^[4,5] Inappropriate and excessive use of antimicrobials, inadequacies in infection prevention and control practices, and deficiencies in surveillance systems create a breeding ground for the selection and spread of resistant strains.^[4] Current global estimates indicate that AMR is associated with millions of deaths annually, and this burden is projected to increase substantially over the coming decades unless effective preventive and control measures are implemented.^[6,7]

Türkiye is among the countries with high AMR rates.^[6,8] In addition, antibiotic-resistant infections are responsible for tens of thousands of deaths each year in European Union countries. In this context, systematic evaluation of the incidence of HAIs, infection types, causative microorganism distribution, and antimicrobial susceptibility profiles in ICUs are critically important for both rationally planning empirical treatment approaches and developing targeted infection control programs.

This study aims to comprehensively analyze the epidemiological characteristics of HAIs developing in ICUs and the AMR patterns of the causative microorganisms and to contribute to evidence-based strategies to reduce the infection burden and the spread of resistant strains based on the findings obtained.

MATERIALS AND METHODS

Study Design and Environment

This retrospective, observational study was conducted at the ICU of Yalova Training and Research Hospital between January

1, 2023, and January 1, 2025. The hospital, which provides tertiary healthcare services, has a total of 44 ICU beds during the study period, including 34 tertiary and 10 secondary level beds. Infection surveillance in ICUs is carried out daily by the Infection Control Committee using an active surveillance method, and all data are regularly recorded.

Study Population

All patients followed in ICU during the study period were included in the evaluation. However, patients followed in the ICU for <1 day and cases with only colonization were excluded from the study.

Data Collection and Definitions

In this study, the total number of hospitalized patients, the number of patient-days, the number of HAIs, the rates of invasive device use, isolated pathogenic micro-organisms, and their AMR profiles were analyzed. HAI definitions were established based on the Centers for Disease Control and Prevention criteria and the National Healthcare-Associated Infections Surveillance Network (USHIESA) diagnostic criteria.^[9,10] In cases where members of the skin flora, such as coagulase-negative staphylococci, were isolated, the patient's clinical findings and laboratory parameters were evaluated in detail. Single positive blood culture was considered contamination in cases without clinical findings suggestive of infection and/or an increase in acute phase reactants. Blood cultures were taken in two sets, and if growth was observed in only one set while appropriate clinical findings were not present, the result was interpreted as contamination. Microorganisms were identified using an automated identification system (VITEK®). Antimicrobial susceptibility testing was performed and interpreted according to the criteria established by the European Committee on Antimicrobial Susceptibility Testing.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA) statistical package program. The invasive device-associated HAI (DA-HAI) rate was calculated by multiplying the ratio of the number of DA-HAIs developing in the relevant period to the total number of hospitalized patients by 100 (DA-HAI rate=[number of DA-HAIs developing/number of hospitalized patients]×100). Invasive device-related infection rates were calculated by multiplying the ratio of the number of DA-HAIs developing in the relevant period to the relevant device-day by 1000 (rate=[number of DA-HAIs developing/device-day]×1000).

Ethical Approval

Ethical approval for the study was obtained from the Yalova University Ethics Committees Coordination Office (Decision

No: 2025/176, Date: 07.05.2025). The study was conducted in accordance with the principles of the Helsinki Declaration.

RESULTS

A total of 6,152 patients were followed up in ICUs for 28,129 patient-days during the study period. Data obtained on the total number of invasive device days used in the ICU during this period were as follows: 25,123 urinary catheter days, 9,825 central venous catheter days, and 3,993 ventilator days. The total rate of HAIs developing in the ICU was determined to be 0.40% (25/6,152). The incidence density of HAIs was found to be 0.88/1000 patient-days (25/28,129). Invasive device usage rates, types of infections developed, and comparative analyses with USHIESA 2024 national reference data are presented in Table 1.

When the distribution of developing HAIs was examined, it was determined that 24 cases (96.0%) were catheter-associated urinary tract infection (CAUTI) and 1 case (4.0%) was central line-associated bloodstream infection (CLABSI). No cases of ventilator-associated pneumonia (VAP) were observed during the study period (Table 1).

Microbiological evaluation revealed that 76.0% of the isolated pathogens were Gram-negative bacteria (GNB) and 24.0% were Gram-positive bacteria (GPB). The most frequently isolated GNBs were *Myroides* spp. (47.36%), *Acinetobacter baumannii* (26.31%), *Klebsiella pneumoniae* (21.05%), and *Pseudomonas aeruginosa* (5.26%), respectively. The proportion of *Myroides* spp. among all 25 HAI isolates was 36.0%. All GPBs were found to be caused by *Enterococcus* spp. A detailed distribution of the pathogens causing HAIs is presented in Figure 1. Antimicrobial susceptibility results showed high levels of resistance among HAI isolates (Table 2). GNB, particularly

Table 1. Comparison of invasive device utilization rates and invasive device-related infection rates in intensive care units with USHIESA 2024 data

Parameters	ICU mean	USHIESA 2024 mean
Invasive device utilization ratios		
Urinary catheter utilization ratio	0.89	0.97
Central line utilization ratio	0.34	0.62
Ventilator utilization ratio	0.14	0.53
Device-associated healthcare-associated infection rates*		
Catheter-associated urinary tract infection	0.95	1.0
Central line-associated bloodstream infection	0.10	4.7
Ventilator-associated pneumonia	0	3.9

*Infection rates were calculated per 1,000 device-days. ICU: Intensive care units

Myroides spp., *A. baumannii*, *Klebsiella* spp., and *P. aeruginosa*, exhibited extensive resistance to most tested antibiotics, with several isolates showing 100% resistance to multiple classes (Table 2). Among GPB, *Enterococcus* spp. demonstrated high resistance to ampicillin, gentamicin, and levofloxacin, while reduced susceptibility to vancomycin and teicoplanin was observed; linezolid remained fully active (Table 2).

DISCUSSION

Despite all advances in medicine and healthcare, HAIs remain a major public health problem, particularly in ICUs, where they are among the most common causes of morbidity and

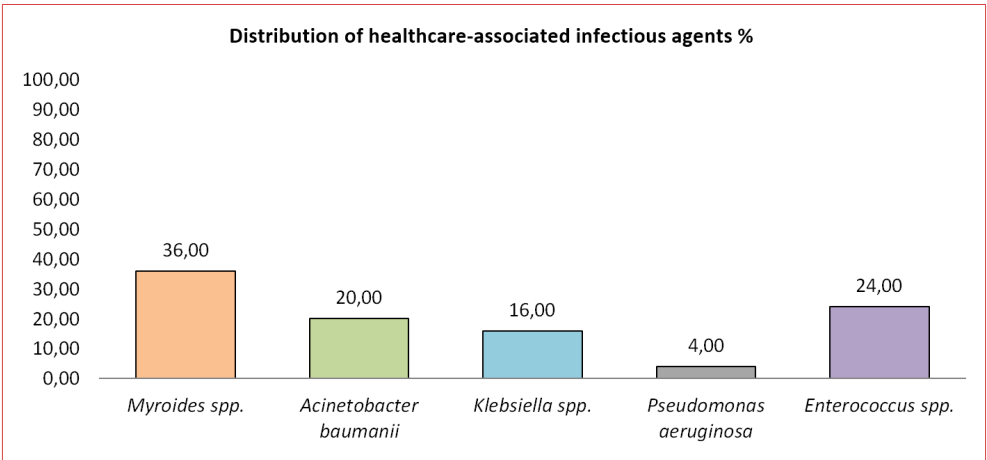


Figure 1. Distribution of pathogens causing healthcare-associated infections developing in the intensive care unit (%).

Table 2. Antimicrobial resistance rates of healthcare-associated infectious agents (%)

Gram-negative bacteria															
Microorganism	CRO	CAZ	FEP	CXM	AMP	CIP	AK	GN	TZP	ETP	IMP	MEM	TGC	SXT	ATM
<i>Myroides</i> spp.	3 (100)	9 (100)	–	–	–	9 (100)	–	9 (100)	9 (100)	–	9 (100)	–	–	9 (100)	9 (100)
<i>Acinetobacter baumannii</i>	2 (100)	–	–	–	–	5 (100)	–	2 (100)	5 (100)	–	5 (100)	3 (75)	3 (100)	5 (100)	–
<i>Klebsiella</i> spp.	4 (100)	4 (100)	4 (100)	4 (100)	3 (100)	4 (100)	2 (50)	4 (100)	4 (100)	3 (75)	3 (75)	–	–	2 (50)	2 (100)
<i>Pseudomonas aeruginosa</i>	1 (100)	1 (100)	–	–	–	1 (100)	–	–	1 (100)	–	1 (100)	1 (100)	–	–	–
Gram-positive bacteria															
Microorganism	AMP	GN	LEV	VAN	TEC	LNZ									
<i>Enterococcus</i> spp.	5 (83)	3 (100)	5 (100)	1 (20)	1 (33)	0									

CRO: Ceftriaxone, CAZ: Ceftazidime, FEP: Cefepime, CXM: Cefuroxime axetil, AMP: Ampicillin, CIP: Ciprofloxacin, AK: Amikacin, GN: Gentamicin, TZP: Piperacillin-tazobactam, ETP: Ertapenem, IMP: Imipenem, MEM: Meropenem, TGC: Tigecycline, SXT: Trimethoprim-sulfamethoxazole, ATM: Aztreonam, LEV: Levofloxacin, VAN: Vancomycin, TEC: Teicoplanin, LNZ: Linezolid. “–”: Not tested

mortality.^[11] This increase in HAI incidence further highlights the importance of strategies aimed at the prevention and control of infections. Determining the incidence of HAIs in ICUs, invasive device utilization ratios, distribution of causative pathogens, and antibiotic susceptibility profiles is crucial for the appropriate planning of empirical treatment approaches.^[12] In this study, the epidemiological characteristics of HAIs developing in the ICU and AMR rates were evaluated.

HAI rates may vary across countries, regions, and hospitals due to differences in patient profiles, care processes, frequency of invasive procedures, and surveillance methods.^[12] According to the 2021 epidemiological report published by the European Centre for Disease Prevention and Control (ECDC), at least one ICU-acquired HAI was reported in 15.6% of patients who stayed in the ICU for more than 2 days.^[13] In a meta-analysis examining the burden and determinants of HAIs in ICUs in Sub-Saharan Africa, the prevalence of HAIs was found to be 28.22% (95% confidence interval [CI]: 23.61–32.81), while a study conducted in Saudi Arabia reported an ICU HAI prevalence of 15.38%.^[14,15] Studies conducted in Türkiye have shown that HAI rates range between 1.2% and 11.48%.^[16,17] In the present study, the HAI rate in ICUs was determined to be 0.40%. Compared with the literature, the relatively low HAI rate may be attributed to the effectiveness of infection control practices in our center as well as differences in patient characteristics and device utilization profiles.

In our study, the majority of HAI cases consisted of CAUTI (96%); only one case of CLABSI was identified, and no cases

of VAP were observed. According to the report of the ECDC (2021), among HAIs developing in ICUs, 10% were pneumonia, 8% were bloodstream infections, and 4% were urinary tract infections; of these, 66% of pneumonia cases were VAP, 38% of bloodstream infections were CLABSI, and 97% of urinary tract infections were CAUTI.^[13] According to data from the International Nosocomial Infection Control Consortium (INICC), the rates per 1,000 device-days in ICUs were reported as 11.96 for VAP, 2.91 for CAUTI, and 4.55 for CLABSI.^[18] In a study conducted by Izadi et al.,^[19] the most common infections in ICUs were reported to be urinary tract infections (19.76%; 19.09/1000 patients, and 3.32/1000 patient-days), followed by pneumonia (15.21%; 14.69/1000 patients, and 2.55/1000 patient-days) and bloodstream infections (13.23%; 12.78/1000 patients, and 2.22/1000 patient-days).

The absence of VAP cases in our study is a noteworthy finding. This observation may be attributed to increased awareness and improved adherence to infection control measures among healthcare workers. In particular, heightened attention to hand hygiene, strict compliance with ventilator care bundles, and more consistent implementation of infection prevention protocols may have contributed to this outcome. Furthermore, sustained behavioral changes and strengthened infection control practices, especially during and after the COVID-19 period, may have played a significant role in reducing the risk of VAP development in our ICUs.

In a meta-analysis by Odoom and Donkor, the prevalence distribution of ICU-acquired HAIs was reported as 54.0%

(95% CI 31.0–76.0%, $I^2=98\%$, $p<0.01$) for VAP, 34.0% (95% CI 25.0–42.0%, $I^2=98\%$, $p<0.01$) for bloodstream infections, and 26.0% (95% CI 17.0–35.0%, $I^2=98\%$, $p<0.01$) for urinary tract infections.^[20] Similarly, studies conducted in our country have shown variability in the distribution; infection rates per 1,000 device-days were highest for VAP (4.5), followed by CAUTI (0.3) and CLABSI (0.2).^[16] In addition, in the study by Güleç and Benlican, the rates were reported as 12.45% for VAP, 8.26% for CLABSI, and 0.48% for CAUTI.^[21] These findings indicate that the distribution of infections in ICUs may vary considerably between centers depending on patient characteristics, frequency of invasive procedures, device utilization ratios, and infection control practices.

In a study conducted by the INICC, across 398 ICUs in China, which evaluated device-associated infections and causative microorganisms, the most frequently isolated pathogen was *A. baumannii* (19.1%), followed by *P. aeruginosa* (17.2%), *K. pneumoniae* (11.9%), and *Staphylococcus aureus* (11.9%).^[22] The leading HAI pathogens were *K. pneumoniae* (16.4%), *A. baumannii* (14.4%), *S. aureus* (11.8%), and *Escherichia coli* (11.4%).^[23] In a multicenter study conducted in southern Poland. A study performed in an ICU in Aljouf, Saudi Arabia, reported *K. pneumoniae* (35.0%) and *A. baumannii* (27.5%), pathogens frequently associated with multidrug resistance, as the most commonly isolated agents.^[15] In a study conducted in Türkiye, *Pseudomonas* spp. (30.4%) was the most prevalent HAI pathogen, followed by *Acinetobacter* spp. (14.3%), *E. coli* (12.5%), *S. aureus* (7.2%), *K. pneumoniae* (5.3%), *Candida albicans* (5.3%), and *Candida parapsilosis* (5.3%).^[21] Another national study reported that the most frequently isolated pathogens were GNB, primarily *A. baumannii*, *K. pneumoniae*, and *E. coli*.^[16] Similarly, in our study, GNB predominated among HAI cases (76%), with the most frequently isolated microorganisms being *Myroides* spp., *Enterococcus* spp., *A. baumannii*, *Klebsiella* spp., and *P. aeruginosa*. Our findings are consistent with previously reported data, highlighting the prominent role of GNB in ICUs. However, they also suggest that pathogen distribution may vary between centers depending on patient characteristics, antibiotic usage patterns, and infection control practices.

The antimicrobial susceptibility profiles of the HAI isolates demonstrate a concerning burden of multidrug resistance, particularly among GNB (Table 2). Notably, *Myroides* spp., *A. baumannii*, *Klebsiella* spp., and *P. aeruginosa* exhibited high to complete resistance against most tested antibiotic classes, including third- and fourth-generation cephalosporins, fluoroquinolones, and piperacillin-tazobactam, indicating severely limited therapeutic options. Carbapenem resistance was also prominent, especially in *A. baumannii* and *Klebsiella* spp., suggesting the emergence of extensively drug-resistant

phenotypes in the clinical setting. Among GPB, *Enterococcus* spp. showed high resistance to ampicillin, aminoglycosides, and fluoroquinolones, while reduced susceptibility to glycopeptides (vancomycin and teicoplanin) raises concern for the potential development of vancomycin-resistant enterococci; however, linezolid retained full activity. Overall, these findings underscore the dominance of highly resistant nosocomial pathogens and highlight the critical need for continuous surveillance and stringent antimicrobial stewardship strategies to preserve the efficacy of remaining therapeutic agents.

HAIs caused by *Myroides* spp. have been reported particularly in ICU patients who were exposed to invasive procedures, had prolonged hospital stays, and received broad-spectrum antibiotics. The multidrug-resistant nature of these microorganisms limits treatment options and complicates infection control processes. The literature emphasizes that *Myroides* spp. is most often isolated as a colonizing organism, but in an appropriate host and under environmental conditions, it can lead to infection.^[24] In Türkiye, Kutlu et al.,^[25] reported an outbreak of six urinary tract infections caused by *Myroides odoratimimus* in an ICU. In another study conducted in an adult ICU, nine *Myroides* spp. isolates were identified over a 3-month period; seven of these were associated with pyuria, while two isolates were considered colonization.^[24] In the study by Gülmez et al.,^[26] among 228 patients with *Myroides* spp. isolates, asymptomatic bacteriuria was detected in 210 cases (92.1%), whereas only 18 cases (7.9%) were associated with true infection. All patients had indwelling catheters in a study evaluating 36 ICU patients from whom *Myroides* spp. was isolated from urinary catheters. After catheter replacement, follow-up control cultures showed persistent growth in only four patients, while no growth was detected in cultures at 24- and 72-h intervals in the remaining patients. The investigators emphasized that in patients with prolonged hospitalization and urinary catheter use, the organism may predominantly lead to colonization; therefore, catheter replacement, careful monitoring of clinical symptoms, and avoidance of unnecessary antimicrobial therapy are critical.^[27] In our study, *Myroides* spp. was the most frequently isolated pathogen among HAIs (47.36%). During the study period, a marked increase in *Myroides* spp. isolation was observed in the ICU, prompting rapid implementation of infection control screening and initiation of a source investigation. Subsequent analysis suggested that a potential association with urine collection containers, and comprehensive infection control interventions successfully contained the situation before it could develop into a large-scale outbreak. These findings demonstrate that, although a rare pathogen, *Myroides* spp. has the potential to cause outbreaks in ICU settings under

favorable conditions, highlighting the critical importance of early surveillance and effective infection control practices. The relatively high frequency of *Myroides* spp. in our ICU may also be associated with potential environmental sources, particularly contamination of urine collection containers, as well as patient-related factors such as prolonged catheterization, extended ICU stay, and prior exposure to broad-spectrum antibiotics, which may facilitate colonization and subsequent infection.

Limitations

The study's limitations include its single-center and retrospective design, limited case numbers, and the absence of molecular type determination. These factors restrict the generalizability of the findings and a complete assessment of the outbreak dynamics of the pathogens. However, the systematic investigation of the role of the rare and multidrug-resistant *Myroides* spp. in ICU infections, the rapid response to the increase in isolations, and the presentation of comparative data with the literature constitute the study's strengths.

CONCLUSION

HAIs in ICUs remain an important patient safety concern. In this study, the observed lower HAI rate compared with the literature suggests the effectiveness of infection control practices; however, the distribution of infection types and causative organisms varies across centers. The predominance of CAUTIs and GNB highlights the need for strict surveillance of invasive device use and AMR. The emergence of *Myroides* spp. as a predominant pathogen further emphasizes the outbreak potential of uncommon opportunistic organisms. Overall, continuous surveillance, rational antibiotic use, and strict infection control measures are essential to reduce the burden of HAIs in ICU settings.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Yalova University Ethics Committee (No: 2025/176, Date: 07/05/2025).

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RH; Materials – GK, EYE, BGG, SK, HIK, ZE, HE, SA, DO, SS, MO, RH; Data collection &/or processing – EYE, HIK, GK; Analysis and/or interpretation – GK, EYE, BGG, SK, HIK, ZE, HE, SA, DO, SS, MO, RH; Literature search – GK, EYE, BGG, SK, HIK, ZE, HE, SA, DO, SS, MO, RH; Writing – GK, EYE, BGG, SK, HIK, ZE, HE, SA, DO, SS, MO, RH; Critical review – GK, EYE, BGG, SK, HIK, ZE, HE, SA, DO, SS, MO, RH.

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Concordance of Gleason Score and Prognostic Grade Group Between Transrectal Ultrasound-Guided Biopsy and Radical Prostatectomy

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ABSTRACT

Objective: Grading discordance between transrectal ultrasound (TRUS)-guided biopsy and radical prostatectomy (RP) specimens represents a clinically significant challenge in prostate cancer management. This study aimed to evaluate the concordance of Gleason score (GS) and prognostic grade group (GG) between TRUS-guided biopsy and RP specimens, and to identify histopathological parameters associated with grading discordance.

Materials and Methods: This retrospective study included 88 patients who underwent TRUS-guided biopsy followed by RP between 2023 and 2026. All biopsy and RP specimens were re-evaluated by two pathologists according to 2019 ISUP consensus criteria. Grading changes were classified as concordant, upgraded, or downgraded. Cohen's kappa coefficient and Spearman correlation were used to assess agreement and correlation. Clinicopathological parameters associated with GG change were analyzed using Chi-square and Fisher's exact tests.

Results: The mean patient age was 66.41 ± 6.5 years. GS and GG concordance was 64.8% (n=57), upgrading was observed in 29.5% (n=26), and downgrading in 5.7% (n=5). Moderate agreement was found for both GS ($\kappa=0.458$) and GG ($\kappa=0.456$), with significant positive correlations (Spearman $\rho=0.680$ and 0.703 , respectively; $p<0.001$). Biopsy tumor volume ($p=0.005$), perineural invasion ($p=0.044$), and pattern 4 ratio ($p=0.028$) were significantly associated with GG change. Among RP parameters, extraprostatic extension ($p=0.002$), perineural invasion ($p=0.006$), surgical margin status ($p=0.021$), and tumor volume ($p=0.018$) were significantly related to grading discordance. Age and pre-biopsy PSA level showed no significant association with GG change.

Conclusion: TRUS-guided biopsy demonstrated moderate concordance with RP specimens. Biopsy-derived parameters including tumor volume, perineural invasion, and pattern 4 ratios provide valuable predictive information for grading discordance. These findings highlight the importance of systematically integrating routine histopathological data into clinical decision-making to optimize patient management.

Keywords: Concordance, Downgrading, Gleason score, Prognostic grade group, Prostate cancer, Radical prostatectomy, Transrectal ultrasound-guided biopsy, Upgrading

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INTRODUCTION

Prostate cancer remains one of the most frequently diagnosed malignancies in men and ranks second among cancer-related causes of death.^[1] The disease represents a heterogeneous group of tumors exhibiting a broad spectrum of biological behavior, which renders risk classification both necessary and challenging.^[1] The Gleason score (GS) and the 2019 International Society of Urological Pathology (ISUP) prognostic grade group (GG) system (GG 1–5) are among the primary tools used in prostate cancer management for determining treatment strategy, selecting between active surveillance and definitive treatment, and conducting prognostic assessment.^[2,3]

Prostate biopsy remains the standard procedure for obtaining diagnosis and performing initial histopathological grading.^[4] Transrectal ultrasound (TRUS)-guided biopsy samples only a limited portion of the prostate gland. This may introduce significant sampling error and lead to grading discordance between biopsy and radical prostatectomy (RP) specimens.^[1] In the literature, GS discordance between biopsy and RP specimens has been reported in 28–76% of cases.^[4] A significant proportion of patients have been found to have grade upgrading following prostatectomy.^[4] When evaluated at the GG level, concordance has been reported to be approximately 54.5%, with upgrading observed in 31.1% and downgrading in 14.3% of cases.^[2]

The clinical significance of this discordance is substantial. Patients undergraded at biopsy may receive insufficient treatment and face a risk of disease progression, whereas overgraded patients may be subjected to unnecessarily aggressive interventions.^[5] Grade upgrading has been identified as an independent predictor of biochemical recurrence following local treatment, even after controlling for known pre-operative variables.^[1] This issue carries particular clinical relevance for active surveillance candidates; patients classified as GG 1 or GG 2 at biopsy may subsequently be found to have higher GGs at prostatectomy.^[6,7]

The pathogenesis of grading discordance is multifactorial. Since TRUS biopsy does not represent the entire prostate gland, there is always a possibility that tumor foci harboring higher Gleason patterns remain unsampled.^[1] Differences in grading approaches between biopsy and prostatectomy specimens may also contribute to discordance. In needle biopsies, GS is typically determined based on the most prevalent and highest-grade pattern due to limited tissue sampling, whereas RP specimens allow more comprehensive evaluation – with the primary and secondary patterns of the dominant tumor focus assessed, and low-proportion high-grade tertiary patterns also reportable.^[8] Tumor multifocality and intratumoral histological heterogeneity are also among

the principal pathological factors that make it difficult to reflect true tumor biology through limited tissue sampling.^[1] Interobserver variability in distinguishing the morphological boundary between Gleason pattern 3 and pattern 4 represents another important source of discordance; although a second pathologist opinion has been shown to improve concordance, it cannot completely eliminate the difference between biopsy and prostatectomy specimens.^[4]

This study aimed to evaluate GS and GG concordance, upgrading and downgrading rates, and the histopathological parameters contributing to grading discordance in patients who underwent TRUS-guided biopsy followed by RP at our institution between 2023 and 2026. The findings were intended to provide an institutional contribution to the grading accuracy of TRUS biopsy and to shed light on pathological evaluation processes.

MATERIALS AND METHODS

Study Design and Case Selection

This study was designed retrospectively on a total of 110 patients who underwent RP at our institution's Department of Pathology between 2023 and 2026 and had matched TRUS biopsy material available. Only patients whose both TRUS biopsy and RP specimens were evaluated at our institution's Department of Pathology were included.

Exclusion criteria were defined as follows: Patients who had received neoadjuvant hormonal therapy or radiotherapy, and patients whose pathology reports were inaccessible. The RP specimen had been evaluated at an external center in 10 patients, and the TRUS biopsy material in seven patients; these cases were therefore excluded from the study. In 5 cases, glass slides and paraffin blocks were unavailable, and these patients were also excluded. As a result, the study was conducted on 88 patients whose both TRUS biopsy and RP materials were accessible from our institution's archive.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the University of Health Sciences, Gaziosmanpaşa Training and Research Hospital, Ethics Committee (Approval No: 82, Date: April 22, 2026).

Histopathological Evaluation

All TRUS biopsy and RP specimens were retrospectively re-evaluated by two pathologists from the archive of our institution's Department of Pathology. TRUS biopsies were assessed using a 12-core scheme.

GS and GG were recorded separately for both materials. Prognostic grade grouping was performed in accordance with

the ISUP consensus criteria.^[3] Cases in which disagreement existed between pathologists were resolved by reaching consensus.

The following histopathological parameters were recorded for both materials: GS, GG, primary and secondary Gleason pattern, tumor volume (%), Gleason pattern 4 ratio (in cases containing pattern 4, expressed as a percentage), and the presence of perineural invasion. Tumor volume was assessed as the percentage of total tumor extent in the relevant material; the pattern 4 ratio was additionally recorded as the percentage of pattern 4 within the tumor in cases containing a Gleason pattern 4 component. The presence of tertiary pattern 5 was also queried separately in both materials.

Additional parameters specific to RP specimens were also evaluated: surgical margin status (positive/negative), extraprostatic extension (EPE), and lymphovascular invasion. All prostatectomy specimens were submitted entirely for histopathological examination in serial sections in accordance with ISUP recommendations.^[9]

Concordance and Correlation Analysis

GS and GG between TRUS biopsy and RP specimens were compared, and cases were classified as follows: unchanged (concordant), upgraded, or downgraded. Cohen's kappa coefficient was used for quantitative measurement of grading concordance; κ values were interpreted as: 0–0.20 poor agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement, and 0.81–1.00 excellent agreement. Spearman correlation analysis was applied to evaluate the ordinal relationship between biopsy and prostatectomy materials.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics 25.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro-Wilk test in conjunction with histogram, Q-Q plot, and boxplot graphs.

In descriptive statistics, continuous variables were presented as mean±standard deviation or median (interquartile range [IQR]) according to their distribution characteristics, and categorical variables were presented as frequency and percentage (*n* [%]). Continuous variables with normal distribution were analyzed using the independent samples t-test, and those without normal distribution were analyzed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test; Fisher's exact test or, in multi-cell tables, the Fisher-Freeman-Halton exact test was applied when expected cell counts were insufficient. A *p*<0.05

was considered statistically significant in all analyses, and all tests were two-tailed.

RESULTS

A total of 88 patients who underwent RP were included in the study. The demographic and clinicopathological characteristics of the patients are summarized in Table 1. The mean age of the patients was 66.41±6.5 years, with an age range of 50–82 years. When evaluated by age group, the majority of patients were in the 55–75 age range (85.2%, *n*=75). The proportion of patients under 55 years was 4.5% (*n*=4), and the proportion of patients over 75 years was 10.2% (*n*=9) (Table 1).

Table 1. Demographic and clinicopathologic characteristics

Variable	Value	Note
Age, years	66.41±6.5	<i>n</i> =88
Age, median (IQR)	66.5 (61.8–71.0)	
Age group		<i>n</i> =88
<55	4 (4.5)	
55–75	75 (85.2)	
>75	9 (10.2)	
Pre-biopsy PSA		<i>n</i> =77
<4	13 (16.9)	
4–10	46 (59.7)	
>10	18 (23.4)	
Post-prostatectomy PSA		<i>n</i> =88
<1	88 (100.0)	
Biopsy Gleason score		<i>n</i> =88
3+3=6	55 (62.5)	
3+4=7	17 (19.3)	
4+3=7	9 (10.2)	
4+4=8	6 (6.8)	
4+5=9	1 (1.1)	
Biopsy GG		<i>n</i> =88
GG 1	55 (62.5)	
GG 2	17 (19.3)	
GG 3	9 (10.2)	
GG 4	6 (6.8)	
GG 5	1 (1.1)	
Biopsy tumor volume		<i>n</i> =88
1–5%	44 (50.0)	
6–10%	14 (15.9)	
11–20%	12 (13.6)	
21–30%	11 (12.5)	

Table 1. Continue

Variable	Value	Note
Biopsy tumor volume		<i>n</i> =88
31–40%	6 (6.8)	
41–50%	1 (1.1)	
Biopsy perineural invasion		<i>n</i> =88
Present	16 (18.2)	
Absent	72 (81.8)	
Biopsy pattern 4 ratio		<i>n</i> =18
6–10%	2 (11.1)	
11–20%	5 (27.8)	
21–30%	4 (22.2)	
31–40%	2 (11.1)	
41–50%	1 (5.6)	
51–60%	1 (5.6)	
61–70%	1 (5.6)	
71–80%	2 (11.1)	
Biopsy tertiary pattern		<i>n</i> =88
Present	2 (2.3)	
Absent	86 (97.7)	
Prostatectomy Gleason score		<i>n</i> =88
3+3=6	38 (43.2)	
3+4=7	27 (30.7)	
4+3=7	14 (15.9)	
4+4=8	6 (6.8)	
4+5=9	3 (3.4)	
Prostatectomy GG		<i>n</i> =88
GG 1	38 (43.2)	
GG 2	29 (33.0)	
GG 3	12 (13.6)	
GG 4	6 (6.8)	
GG 5	3 (3.4)	
Prostatectomy tumor volume		<i>n</i> =88
1–5%	30 (34.1)	
6–10%	12 (13.6)	
11–20%	23 (26.1)	
21–30%	7 (8.0)	
31–40%	8 (9.1)	
41–50%	3 (3.4)	
51–60%	1 (1.1)	
61–70%	1 (1.1)	

Table 1. Continue

Variable	Value	Note
Prostatectomy tumor volume		<i>n</i> =88
71–80%	2 (2.3)	
81–90%	0 (0.0)	
>90%	1 (1.1)	
Surgical margin		<i>n</i> =88
Positive	31 (35.2)	
Negative	57 (64.8)	
Prostatectomy perineural invasion		<i>n</i> =88
Present	54 (61.4)	
Absent	34 (38.6)	
Extraprostatic extension		<i>n</i> =88
Present	21 (23.9)	
Absent	67 (76.1)	
Prostatectomy pattern 4 ratio		<i>n</i> =31
1–5%	2 (6.5)	
6–10%	8 (25.8)	
11–20%	7 (22.6)	
21–30%	6 (19.4)	
31–40%	2 (6.5)	
61–70%	2 (6.5)	
71–80%	2 (6.5)	
81–90%	1 (3.2)	
>90%	1 (3.2)	
Prostatectomy tertiary pattern		<i>n</i> =88
Present	4 (4.5)	
Absent	84 (95.5)	last

Values are presented as mean±SD, median [IQR], or *n* (%). PSA: Prostate-specific antigen, GG: Grade group, PNI: Perineural invasion

When pre-biopsy PSA levels were evaluated, PSA values were below 4 ng/mL in 16.9% (*n*=13), between 4–10 ng/mL in 59.7% (*n*=46), and above 10 ng/mL in 23.4% (*n*=18) of patients. Post-prostatectomy PSA levels were below 1 ng/mL in all cases (100%, *n*=88).

When the GS distribution in TRUS biopsy materials was examined, the most frequently observed score was 3+3=6 (62.5%, *n*=55), followed by 3+4=7 (19.3%, *n*=17), 4+3=7 (10.2%, *n*=9), and 4+4=8 (6.8%, *n*=6); a GS of 4+5=9 was detected in one case (1.1%). With regard to TRUS biopsy GG, 62.5% (*n*=55) of patients were classified as GG 1, 19.3% (*n*=17) as GG 2, 10.2% (*n*=9) as GG 3, 6.8% (*n*=6) as GG 4, and 1.1% (*n*=1) as GG 5.

Tumor volume in TRUS biopsy materials was most frequently observed in the 1–5% range, and this group constituted 50.0% ($n=44$) of all cases. This was followed by patients with a tumor volume of 6–10% (15.9%, $n=14$), 11–20% (13.6%, $n=12$), and 21–30% (12.5%, $n=11$). Perineural invasion was detected in 18.2% ($n=16$) of TRUS biopsy materials, while 81.8% ($n=72$) of cases showed no perineural invasion. Tertiary pattern was present in only 2.3% ($n=2$) of TRUS biopsy materials.

When the GS distribution in RP materials was examined, the most frequently detected score was 3+3=6 (43.2%, $n=38$), followed by 3+4=7 (30.7%, $n=27$), 4+3=7 (15.9%, $n=14$), 4+4=8 (6.8%, $n=6$), and 4+5=9 (3.4%, $n=3$). The GG distribution in RP materials showed that 43.2% ($n=38$) of patients were classified as GG 1, 33.0% ($n=29$) as GG 2, 13.6% ($n=12$) as GG 3, 6.8% ($n=6$) as GG 4, and 3.4% ($n=3$) as GG 5 (Fig. 1).

When tumor volume in RP materials was evaluated, tumor volume was in the 1–5% range in 34.1% ($n=30$), 6–10% in 13.6% ($n=12$), 11–20% in 26.1% ($n=23$), and 21–30% in 8.0% ($n=7$) of patients. Tumor at the surgical margin was observed in 35.2% ($n=31$) of patients, while 64.8% ($n=57$) had negative surgical margins. Perineural invasion was detected in 61.4% ($n=54$) and EPE in 23.9% ($n=21$) of RP materials. Tertiary pattern was present in 4.5% ($n=4$) of cases.

When GS change between TRUS biopsy and RP materials was evaluated, GS remained the same in 64.8% ($n=57$), a higher GS was detected in the RP material in 29.5% ($n=26$) (Fig 2a and b), and a lower GS was observed in 5.7% ($n=5$). Similarly, regarding GG, concordance was noted in 64.8% ($n=57$), upgrading in 29.5% ($n=26$), and downgrading in 5.7% ($n=5$) of cases (Table 2).

When agreement between TRUS biopsy and RP specimens was evaluated using Cohen's kappa coefficient for GS, moderate agreement was found ($\kappa=0.458$). A statistically

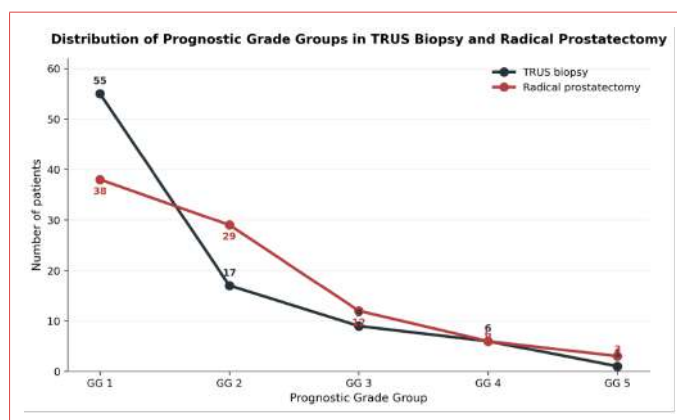


Figure 1. Distribution of prognostic grade groups in transrectal ultrasound biopsy and radical prostatectomy.

significant positive correlation was detected in the correlation analysis between GS values (Spearman $\rho=0.680$, $p<0.001$). Moderate agreement was also observed between biopsy and prostatectomy materials for GG ($\kappa=0.456$). The correlation between GG values was positive and statistically significant (Spearman $\rho=0.703$, $p<0.001$) (Table 3).

When GS change was evaluated by age group, the upgrading rate was 25.0% ($n=1$), and the concordance rate was 75.0% ($n=3$) among patients under 55 years of age. In the 55–75 age group, the upgrading rate was 32.0% ($n=24$), the concordance rate was 62.7% ($n=47$), and the downgrading rate was 5.3% ($n=4$). In patients over 75 years of age, upgrading was observed in 11.1% ($n=1$), concordance in 77.8% ($n=7$), and downgrading in 11.1% ($n=1$). No statistically significant association was found between age groups and GS change ($p=0.685$). The same distribution was observed for GG change, and no significant association was found between age groups and GG change ($p=0.685$).

Table 2. Gleason score on TRUS biopsy and radical prostatectomy with score change

TRUS biopsy	Radical prostatectomy, n (% of TRUS biopsy group)					Change in score, n (% of TRUS biopsy group)			
	3+3=6	3+4=7	4+3=7	4+4=8	4+5=9	Total	Upgraded	Same	Downgraded
3+3=6	36 (65.5)	13 (23.6)	6 (10.9)	0	0	55	19 (34.5)	36 (65.5)	0
3+4=7	2 (11.8)	13 (76.5)	1 (5.9)	1 (5.9)	0	17	2 (11.8)	13 (76.5)	2 (11.8)
4+3=7	0	0	5 (55.6)	3 (33.3)	1 (11.1)	9	4 (44.4)	5 (55.6)	0
4+4=8	0	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	6	1 (16.7)	2 (33.3)	3 (50.0)
4+5=9	0	0	0	0	1 (100.0)	1	0	1 (100.0)	0
Total	38	27	14	6	3	88	26 (29.5)	57 (64.8)	5 (5.7)

Rows represent TRUS biopsy Gleason score; columns represent radical prostatectomy Gleason score. Cell values are n (% of TRUS biopsy group)

Table 3. Agreement statistics between TRUS biopsy and radical prostatectomy				
Comparison	Valid n	Cohen kappa	Spearman rho	p
Gleason score	88	0.458	0.680	<0.001
Prognostic grade group	88	0.456	0.703	<0.001
TRUS: Transrectal ultrasound				

Association of Clinicopathological Parameters with Prognostic GG Change

GG change was compared with age, PSA level, biopsy findings, and histopathological parameters of the prostatectomy material. No significant association was found between age and GG change ($p=0.685$). Similarly, no statistically significant association was detected between pre-biopsy PSA value and GG change ($p=0.373$).

In contrast, statistically significant associations were found between TRUS biopsy GS and TRUS biopsy GG and post-prostatectomy GG change ($p<0.001$ for both). Biopsy tumor volume was also significantly associated with GG change ($p=0.005$). In addition, the presence of perineural invasion in TRUS biopsy material ($p=0.044$) and biopsy pattern 4 ratio ($p=0.028$) were significantly associated with GG change ($p<0.001$).

When parameters from the RP material were evaluated, a significant association was found between prostatectomy GS and prostatectomy GG and GG change ($p<0.001$). Tumor

volume ($p=0.018$), surgical margin status ($p=0.021$), the presence of perineural invasion ($p=0.006$), and EPE ($p=0.002$) in the prostatectomy material were also significantly associated with GG change. A borderline near-significant association was observed between pattern 4 ratio in the prostatectomy material and GG change, but it did not reach statistical significance ($p=0.061$). No significant association was found between tertiary pattern presence in the prostatectomy material and GG change ($p=0.232$) (Table 4).

In this study, approximately two-thirds concordance was observed between TRUS biopsy and RP materials in terms of both GS and GG. However, in approximately one-third of cases, higher GS and GG were detected in the RP material. This finding demonstrates that while TRUS biopsy is an important diagnostic tool in prostate cancer, it may not always fully reflect tumor heterogeneity.

DISCUSSION

Grading discordance between TRUS biopsy and RP in the histopathological assessment of prostate cancer is a long-

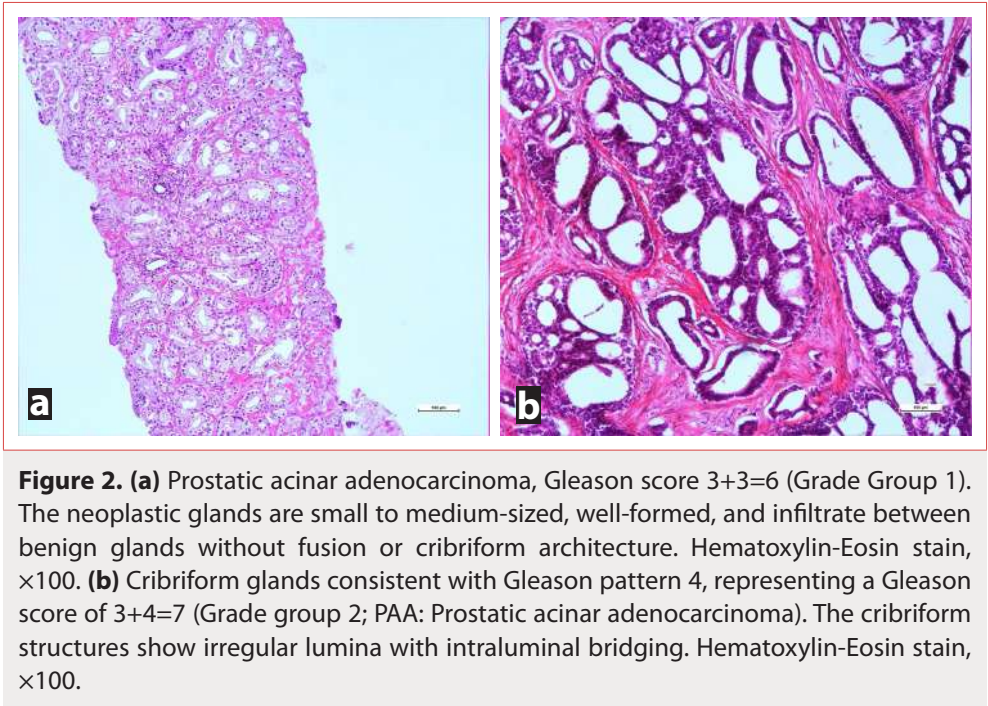


Table 4. Clinicopathologic comparisons according to GG change

Variable	Upgraded n (%)	Same n (%)	Downgraded n (%)	p
Age group				0.685
<55	1 (25.0)	3 (75.0)	0 (0.0)	
55–75	24 (32.0)	47 (62.7)	4 (5.3)	
>75	1 (11.1)	7 (77.8)	1 (11.1)	
Pre-biopsy PSA				0.373
<4	2 (15.4)	9 (69.2)	2 (15.4)	
4–10	13 (28.3)	32 (69.6)	1 (2.2)	
>10	4 (22.2)	12 (66.7)	2 (11.1)	
Biopsy Gleason score				<0.001
3+3=6	19 (34.5)	36 (65.5)	0 (0.0)	
3+4=7	2 (11.8)	13 (76.5)	2 (11.8)	
4+3=7	4 (44.4)	5 (55.6)	0 (0.0)	
4+4=8	1 (16.7)	2 (33.3)	3 (50.0)	
4+5=9	0 (0.0)	1 (100.0)	0 (0.0)	
Biopsy GC				<0.001
GG 1	19 (34.5)	36 (65.5)	0 (0.0)	
GG 2	2 (11.8)	13 (76.5)	2 (11.8)	
GG 3	4 (44.4)	5 (55.6)	0 (0.0)	
GG 4	1 (16.7)	2 (33.3)	3 (50.0)	
GG 5	0 (0.0)	1 (100.0)	0 (0.0)	
Biopsy tumor volume				0.005
1–5%	11 (25.0)	32 (72.7)	1 (2.3)	
6–10%	5 (35.7)	8 (57.1)	1 (7.1)	
11–20%	2 (16.7)	8 (66.7)	2 (16.7)	
21–30%	5 (45.5)	6 (54.5)	0 (0.0)	
31–40%	3 (50.0)	3 (50.0)	0 (0.0)	
41–50%	0 (0.0)	0 (0.0)	1 (100.0)	
Biopsy PNI				0.044
Present	4 (25.0)	9 (56.2)	3 (18.8)	
Absent	22 (30.6)	48 (66.7)	2 (2.8)	
Biopsy pattern 4 ratio				0.028
6–10%	0 (0.0)	2 (100.0)	0 (0.0)	
11–20%	0 (0.0)	5 (100.0)	0 (0.0)	
21–30%	1 (25.0)	3 (75.0)	0 (0.0)	
31–40%	1 (50.0)	1 (50.0)	0 (0.0)	
41–50%	0 (0.0)	1 (100.0)	0 (0.0)	
51–60%	1 (100.0)	0 (0.0)	0 (0.0)	
61–70%	0 (0.0)	0 (0.0)	1 (100.0)	
71–80%	1 (50.0)	1 (50.0)	0 (0.0)	

Table 4. Continue

Variable	Upgraded n (%)	Same n (%)	Downgraded n (%)	p
Biopsy tertiary pattern				0.573
Present	0 (0.0)	2 (100.0)	0 (0.0)	
Absent	26 (30.2)	55 (64.0)	5 (5.8)	
RP Gleason score				<0.001
3+3=6	0 (0.0)	36 (94.7)	2 (5.3)	
3+4=7	13 (48.1)	13 (48.1)	1 (3.7)	
4+3=7	7 (50.0)	5 (35.7)	2 (14.3)	
4+4=8	4 (66.7)	2 (33.3)	0 (0.0)	
4+5=9	2 (66.7)	1 (33.3)	0 (0.0)	
RP GG				<0.001
GG 1	0 (0.0)	36 (94.7)	2 (5.3)	
GG 2	15 (51.7)	13 (44.8)	1 (3.4)	
GG 3	5 (41.7)	5 (41.7)	2 (16.7)	
GG 4	4 (66.7)	2 (33.3)	0 (0.0)	
GG 5	2 (66.7)	1 (33.3)	0 (0.0)	
RP tumor volume				0.018
1–5%	4 (13.3)	25 (83.3)	1 (3.3)	
6–10%	3 (25.0)	9 (75.0)	0 (0.0)	
11–20%	11 (47.8)	11 (47.8)	1 (4.3)	
21–30%	3 (42.9)	3 (42.9)	1 (14.3)	
31–40%	4 (50.0)	3 (37.5)	1 (12.5)	
41–50%	1 (33.3)	2 (66.7)	0 (0.0)	
51–60%	0 (0.0)	1 (100.0)	0 (0.0)	
61–70%	0 (0.0)	1 (100.0)	0 (0.0)	
71–80%	0 (0.0)	2 (100.0)	0 (0.0)	
>90%	0 (0.0)	0 (0.0)	1 (100.0)	
Surgical margin				0.021
Positive	12 (38.7)	15 (48.4)	4 (12.9)	
Negative	14 (24.6)	42 (73.7)	1 (1.8)	
RP PNI				0.006
Present	22 (40.7)	28 (51.9)	4 (7.4)	
Absent	4 (11.8)	29 (85.3)	1 (2.9)	
Extraprostatic extension				0.002
Present	11 (52.4)	7 (33.3)	3 (14.3)	
Absent	15 (22.4)	50 (74.6)	2 (3.0)	
RP pattern 4 ratio				0.061
1–5%	1 (50.0)	1 (50.0)	0 (0.0)	
6–10%	5 (62.5)	3 (37.5)	0 (0.0)	
11–20%	4 (57.1)	3 (42.9)	0 (0.0)	

Table 4. Continue				
Variable	Upgraded n (%)	Same n (%)	Downgraded n (%)	p
RP pattern 4 ratio				0.061
21–30%	3 (50.0)	2 (33.3)	1 (16.7)	
31–40%	0 (0.0)	2 (100.0)	0 (0.0)	
61–70%	2 (100.0)	0 (0.0)	0 (0.0)	
71–80%	0 (0.0)	2 (100.0)	0 (0.0)	
81–90%	0 (0.0)	0 (0.0)	1 (100.0)	
>90%	0 (0.0)	1 (100.0)	0 (0.0)	
RP tertiary pattern				0.232
Present	1 (25.0)	2 (50.0)	1 (25.0)	
Absent	25 (29.8)	55 (65.5)	4 (4.8)	

RP: Radical prostatectomy, PNI: Perineural invasion, GG: Grade group

stands out as the factor showing the strongest association with GG change ($p=0.002$). Upgrading was observed in 52.4% of cases with EPE, a rate clearly above that of cases without EPE (22.4%). This finding once again confirms the well-established relationship between EPE and high-grade tumor biology. Studies in the literature have highlighted the role of pre-operative MRI findings in predicting biopsy-prostatectomy GG concordance and the presence of EPE.^[19] Similarly, surgical margin positivity was also found to be significantly associated with GG change ($p=0.021$). Park et al.^[14] demonstrated that rates of EPE and positive surgical margins were significantly higher in upgraded GS groups. Perineural invasion in the prostatectomy material was also significantly associated with GG change ($p=0.006$), and this parameter has been evaluated as an indicator of aggressiveness associated with recurrence.^[16] Ozkaya et al.^[20] examined the relationship between clinical and histopathological parameters in TRUS biopsies and upgrading across different risk groups, emphasizing that biopsy-derived features play an important role in determining the risk of upgrading.

Age and pre-operative PSA level showed no statistically significant association with GG change in our study ($p=0.685$ and $p=0.373$, respectively). The independent predictive role of PSA is debated in the literature; while some studies have identified PSA as an independent determinant of GS upgrading,^[11] others have shown that PSA's contribution weakens when evaluated together with biopsy-derived parameters.^[6] The fact that only four patients were under 55 years of age in our series limited reliable statistical evaluation of this subgroup.

This study has some methodological limitations. Due to its retrospective design, selection bias and unobserved

confounding variables may have affected the analysis. The number of patients included reduced statistical power, particularly in higher GG subgroups. Since all patients received standard 12-core TRUS systematic biopsy, comparison with mpMRI fusion biopsy was not possible. The literature has demonstrated that combined biopsy approaches significantly increase concordance and reduce upgrading rates compared to TRUS systematic biopsy.^[7] Furthermore, data on prostate volume, PSA density, and tumor multifocality could not be included in the analyses, limiting the evaluation of potential confounding variables.

CONCLUSION

This study demonstrates that parameters already present in the routine pathology report – tumor volume, perineural invasion, and pattern 4 ratio – provide valuable information for predicting grading concordance. These findings emphasize the importance of systematically incorporating existing histopathological data into treatment decisions without requiring additional technical investment. Given that grading discordance cannot be completely prevented, it is considered that a multidisciplinary approach in which clinicians and pathologists jointly interpret these parameters will play a decisive role in post-biopsy patient management.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Gaziosmanpasa Training and Research Hospital Ethics Committee (No: 82, Date: 22/04/2026).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Influenza and Pneumococcal Vaccination Awareness and Uptake in Adults With Diabetes: Impact of the COVID-19 Pandemic

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ABSTRACT

Objective: Influenza (IV) and pneumococcal (PV) vaccination rates have been reported as suboptimal among patients with diabetes before the COVID-19 pandemic. This study aimed to evaluate IV and PV uptake before and during the pandemic and to assess whether awareness and attitudes toward routine vaccinations changed.

Materials and Methods: We conducted a single-center, paired within-subject study that included patients with diabetes who attended Internal Medicine and Endocrinology outpatient clinics between October 2022 and April 2023. The same patient group was evaluated, and their IV and PV status, awareness, and attitudes toward vaccination during both pre-pandemic and pandemic periods were assessed and compared to determine temporal changes.

Results: Among 515 diabetic patients (62% female, mean age of 59±11 years), IV increased from 27.7% to 40.7%, and PV rose from 11.4% to 18.4% (both $p<0.001$). Awareness of routine adult vaccinations increased substantially during the pandemic, rising from 32% to 54% for IV and from 15% to 28% for PV ($p<0.001$). During the pandemic, older age, longer diabetes duration, prior IV, history of COVID-19, and receipt of COVID-19 vaccine independently predicted IV; older age and prior COVID-19 predicted PV. Despite gains, 46% remained unaware of recommended IV and/or PV by the end of 2021.

Conclusion: Our results are particularly valuable in highlighting the increased awareness and risk perception during the pandemic, which contributed to a rise in routine vaccination uptake among diabetic patients. However, the IV and PV coverage rates among diabetic patients remained below the targets recommended by the World Health Organization.

Keywords: COVID-19 pandemic, Diabetes mellitus, Influenza vaccines, Pneumococcal vaccines, Vaccination awareness

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INTRODUCTION

In December 2019, an infection caused by a new type of coronavirus (SARS-CoV-2) was identified in Wuhan, Hubei Province, China, causing an epidemic with a clinical presentation similar to viral pneumonia. As the COVID-19 outbreak escalated into a pandemic, various quarantine measures were implemented. Consequently, outpatient healthcare services and elective surgical procedures were suspended in many healthcare institutions to prioritize the care of the growing number of COVID-19 cases. During the quarantine, routine follow-up and care of at-risk groups, such as diabetic patients, were impacted, including the interruption of routine influenza and pneumococcal immunization practices.

The development and widespread administration of COVID-19 vaccines heightened public awareness of vaccination as a critical strategy for preventing infectious diseases. Even though efforts were focused on combating the COVID-19 pandemic, concerns emerged regarding the simultaneous resurgence of other vaccine-preventable diseases (e.g., influenza and pneumococcal infection), which might increase morbidity and mortality, particularly among vulnerable groups, and further strain healthcare systems. Although early World Health Organization (WHO) recommendations call for careful risk-benefit analysis regarding continuation of the immunization services during COVID-19, the U.S. centers for disease control and prevention issued clear guidance advocating for the uninterrupted delivery of all routine vaccinations.^[1,2]

Influenza (IV) and pneumococcal (PV) vaccinations are particularly important in the primary care of diabetic patients, given their increased susceptibility to severe respiratory infections. However, data regarding the pandemic's impact on vaccination coverage remains limited. Social distancing policies, decreased healthcare service capacity, and reduced routine clinical visits were expected to result in lower uptake of IV and PV. Interestingly, an increased demand for these vaccines, along with COVID 19 vaccine, was observed during the early pandemic among both diabetic and non-diabetic patients. Understanding the epidemiological dynamics of routine vaccinations during the pandemic, which can influence vaccination rates, may help identify factors that contribute to the success of future vaccination campaigns. This study aimed to evaluate the rates of IV and PV among diabetic patients during the COVID-19 pandemic and compare them with pre-pandemic rates to assess whether/how the pandemic-related precautionary measures influenced risk perception, knowledge, and attitudes toward these vaccines in the high-risk population.

MATERIALS AND METHODS

Study Design

This was a single-center study with a retrospective within-subject (paired) design conducted among patients with diabetes mellitus (DM) at the Department of Internal Medicine and Endocrinology outpatient clinics between October 2022 and April 2023.

Participants

Patients with Type 1 (T1DM) and Type 2 (T2DM) DM over age 18 who attended the internal medicine and endocrinology outpatient clinics, provided informed consent for data collection, and had no contraindications to vaccination were consecutively included in the study. Exclusion criteria included gestational diabetes, inability to provide reliable vaccination information, and refusal to participate.

Data Collection and Measurements

All patients were evaluated during a single study visit, conducted between October 10, 2022, and April 10, 2023. Sociodemographic data (age, marital and education status), comorbid diseases (hypertension, coronary artery disease, cerebrovascular disease, chronic kidney damage, asthma, chronic obstructive pulmonary disease [COPD]), type of diabetes, and disease duration were recorded for all the patients included in the study. We use the term "chronic pulmonary disease (CPD)" to refer to patients with asthma and COPD. A history of COVID-19 infection and vaccination status was determined for all participants. Additionally, patients were surveyed regarding their knowledge and perceptions of COVID-19, including: (i) awareness of its infectious nature and associated health risks (risk perception), (ii) understanding of respiratory transmission, and (iii) knowledge of vaccine-preventable aspects and perceived benefits of COVID-19 vaccination.

For the purposes of this study, the period from January 2019 to March 2020 was defined as the pre-pandemic period, and the period from March 2020 to the end of 2021 as the (early) pandemic period. Each participant within the same group of DM patients was evaluated for routine vaccination across both time periods. Although data collection and patient interviews were conducted during a single visit, participants were asked retrospectively to report their IV and PV status, as well as their awareness and attitudes toward vaccination, for both the early pre-pandemic and pandemic periods. This design allowed for a within-subject comparison, enabling the evaluation of temporal changes in vaccination behavior, awareness, and attitudes within the same group of diabetic patients. Vaccine uptake information was obtained from patient self-reports and/or electronic medical records. Whenever possible, all patient-reported information was cross-checked against

electronic medical records to ensure accuracy. In cases where patient-reported data were inconsistent with electronic records, the latter were considered the primary source. For PV, participants were asked whether they had received a PV within the preceding 5 years, and during both study periods.

The primary source of vaccination information (healthcare professionals, close social contacts, or media) was also identified for each period. The main reasons for non-vaccination were investigated, including lack of belief in vaccine efficacy, vaccine negligence or hesitancy, fear of side effects, and anti-vaccine attitudes among vaccine-aware diabetics. Patients were asked whether their attitudes toward IV and PV had changed during the COVID-19 pandemic and subsequent vaccination campaigns. After being informed about the potential health benefits of IV and PV in diabetes, their willingness to receive vaccination was also assessed. Finally, factors associated with vaccination uptake among diabetic patients during both study periods were analyzed.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables were expressed as mean±standard deviation, and comparisons between two groups were performed using the Student's *t*-test or the Mann–Whitney U test, depending on the normality of data distribution. Categorical variables were compared using the Chi-square test. For non-normally distributed data, comparisons were conducted using the Wilcoxon Signed-Rank test. For paired categorical comparisons within the same cohort across 2 time points, McNemar's test was applied. Comparisons across multiple groups were carried out using the Kruskal–Wallis test, followed by Dunn's *post hoc* test to identify pairwise differences. Multivariate logistic regression analysis was performed to identify independent predictors of vaccination uptake. A *p*<0.05 was assumed for statistical significance in all tests. Data were analyzed with the Statistical Package for the Social Sciences (SPSS) 21.0 (SPSS Inc. Chicago, IL, USA).

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. Approval was first obtained from our hospital's Education Planning Committee. Subsequently, the study received ethical approval from the Institutional Ethics Committee of University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital (Date: October 03, 2022; Decision No: E-48670771–514.99). Written informed consent was obtained from all participants. Participant confidentiality and data privacy were strictly maintained; all personal identifiers were removed from the dataset, and data were stored securely with access limited to the research team.

RESULTS

A total of 544 patients with diabetes (T1DM and T2DM) were screened. After excluding 20 participants who provided incomplete information and 9 who declined participation, 515 patients were included in the final analysis. Sociodemographic and clinical characteristics are summarized in Table 1.

COVID-19 Awareness

Of the study population, 57% recognized COVID-19 as an infectious disease with high mortality risk, 60% understood its respiratory transmission, and 87% were aware that it is vaccine-preventable. Thirteen percent reported unwillingness to receive the COVID-19 vaccine.

Table 1. Demographic and clinical characteristics of patients with diabetes mellitus (n=515)

Variables	n=515
Age (mean±SD, range)	59.3±11.9 (26–90)
Gender n, (%)	
Female/male	317 (62)/198 (38)
Marital state/life style n, (%)	
Married or living with family	402 (78)
Single/living alone	113 (22)
Education n, (%)	
Illiterate	77 (15)
Primary school	169 (33)
Middle school	122 (24)
High school	87 (17)
University	60 (11)
Diabetes duration (year; mean±SD, range)	11.8±6.3 (5–50)
Type of diabetes n, (%)	
Type 1 diabetes mellitus	36 (7)
Type 2 diabetes mellitus	479 (93)
Comorbidities n, (%)	404 (78)
Hypertension	386 (75)
Coronary artery disease	177 (34)
Cerebrovascular disease	12 (2)
Chronic kidney disease	85 (16)
Chronic pulmonary disease	85 (16)
A history of COVID-19 infection n, (%)	165 (32)
COVID-19 vaccination n, (%)	450 (87)

SD: Standard deviation

Awareness and Uptake of IV and PV

Awareness of IV among diabetics increased from 32% to 54%, corresponding to 113 (22%) newly informed patients. Pre-pandemic, 87% of IV-aware patients ($n=164$) were vaccinated compared with 76% of 277 IV-aware patients during the pandemic (Table 2 and Fig. 1).

Among the same group of 515 participants, the IV rate increased significantly from 27.8% before the pandemic to 40.7% during the pandemic ($p<0.001$, McNemar test; (Table 2; Figs 1 and 2). Specifically, 71 individuals who had not been vaccinated before the pandemic received the IV during the pandemic, whereas only 4 previously vaccinated participants did not continue vaccination. A comparative distribution of IV status before and during the pandemic is illustrated in Figure 2.

During the pandemic, awareness and uptake of PV increased concurrently (Table 2 and Fig. 1). After excluding patients vaccinated before the study period, PV uptake approximately doubled compared with the pre-pandemic period (Table 2).

Lack of awareness remained the leading reason for non-vaccination across both periods. During the pandemic, vaccine-aware but unvaccinated patients most commonly cited safety concerns, while pre-pandemic non-vaccination was mainly due to neglect (Fig. 3). Healthcare workers were the primary sources of information for both IV and PV in the pre-pandemic and pandemic periods (Fig. 4).

Changes in Attitudes toward Routine Vaccination

Among 279 diabetic patients who were informed about IV or PV during the pandemic, 66% maintained a positive attitude toward routine vaccinations in both periods, 11% reported a positive change during the pandemic, and 7% shifted from positive to negative attitudes despite prior COVID-19. Despite prior vaccination, 45 (16%) patients (16%) maintained a

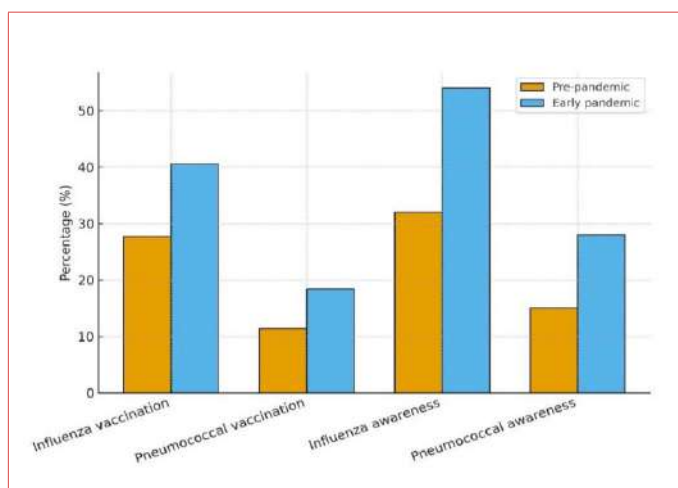


Figure 1. Comparison of vaccination awareness and rates, pre-pandemic versus pandemic.

negative attitude during the pandemic. Following physician counseling, 81% of previously unaware patients expressed willingness to receive IV and/or PV.

Evaluation of Sociodemographic Factors and COVID-19-Related Factors Influencing IV and PV

Factors influencing IV rates were similar in both (pre-pandemic and pandemic) periods (Table 3). The only gender difference observed in pre-pandemic IV was equalized during the pandemic. Those who received the IV were more likely to accept the COVID-19 vaccine as well. Similarly, sociodemographic factors affecting PV rates were similar in both pre-pandemic and pandemic periods (Table 4). It was determined that 97% of the participants who were vaccinated against pneumococcus during the pandemic also had IV during the pandemic period. Most of them had IV in the pre-pandemic period. In our study, it was observed that higher education was associated with

Table 2. Changes in vaccination rates and awareness between pre-pandemic and pandemic times in the same group of adults with diabetes mellitus

Variables	Pre-pandemic period January 2019–March 2020	Pandemic period March 22–December 2021	Absolute Δ pp	p
A total number of patients $n=515$				
Influenza vaccination rate $n, (\%)$	143 (27.7)	210 (40.7)	+13.0	<0.001*
Pneumococcal vaccination rate $n, (\%)$	59 (11.4)	95 (18.4)	+7.0	<0.001*
	20 (3.9)*	36 (7.8)**		
Influenza vaccine awareness $n, (\%)$	164 (32)	277 (54)	+22.0	<0.001*
Pneumococcal vaccine awareness $n, (\%)$	78 (15)	144 (28)	+13.0	<0.001*

Data are paired within-cohort comparisons. Absolute Δ pp denotes percentage-point change from pre-pandemic to early pandemic period. *20 (3.9) vaccinated in 2019, **36 (7.8) newly vaccinated in 2020 Newly vaccinated" refers to participants who had not received a pneumococcal vaccine before the pandemic period but received at least one pneumococcal vaccine during the pandemic period

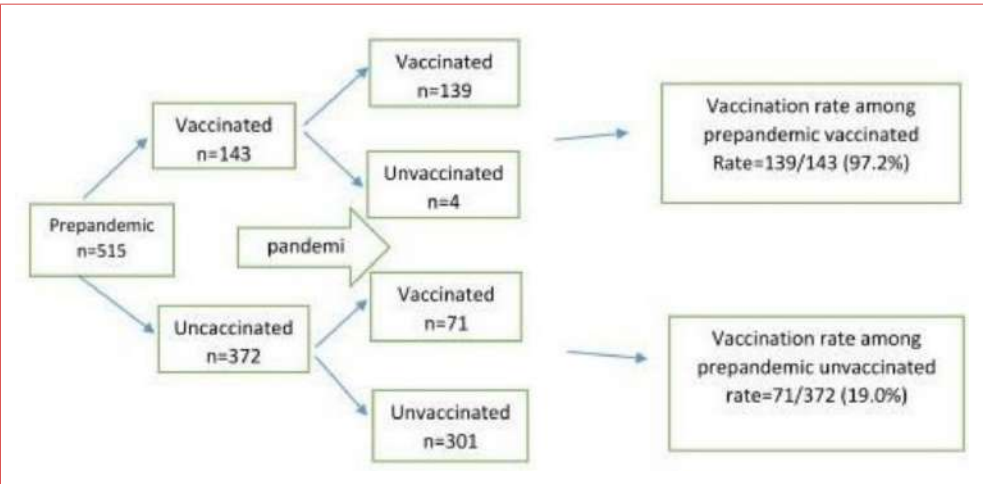


Figure 2. Comparison of influenza vaccination status before and during the COVID-19 pandemic (McNemar: $\chi^2(1)=58.08, p<0.00$).

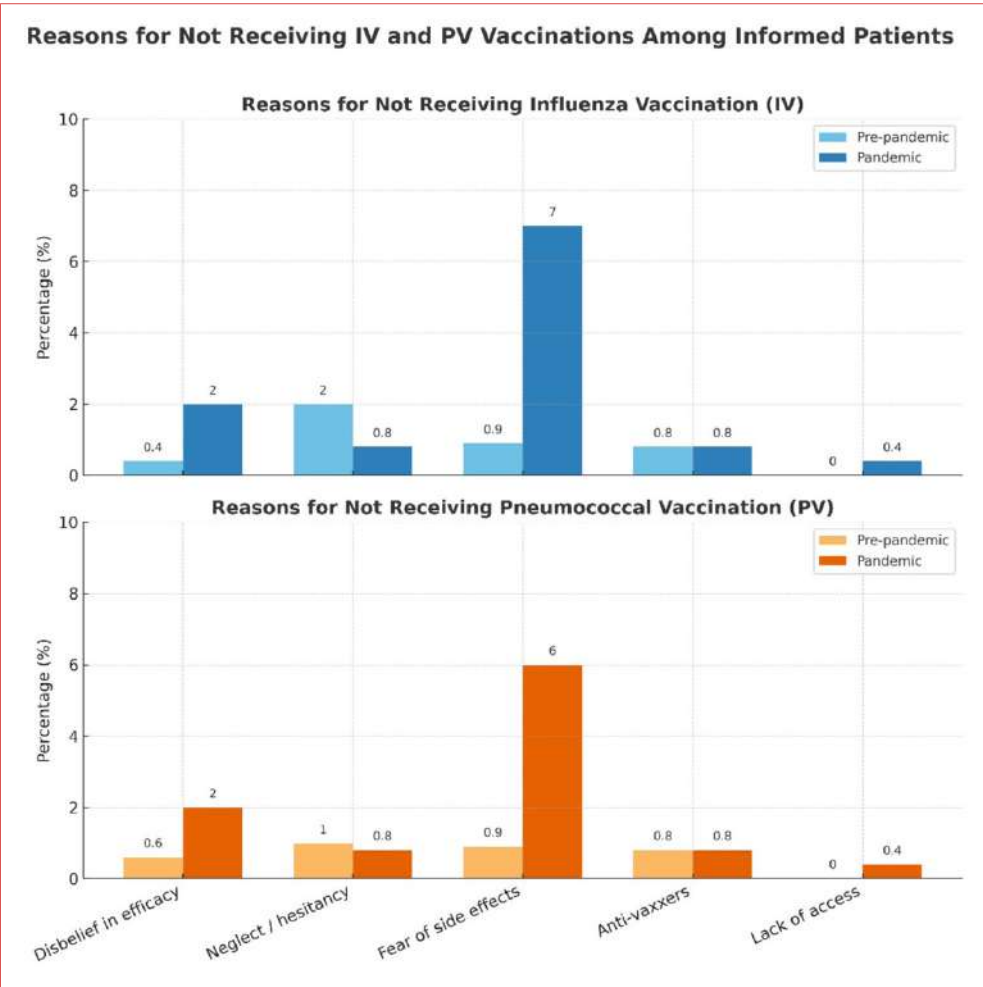


Figure 3. Reasons for not receiving influenza and pneumococcal vaccinations among vaccine-aware patients.

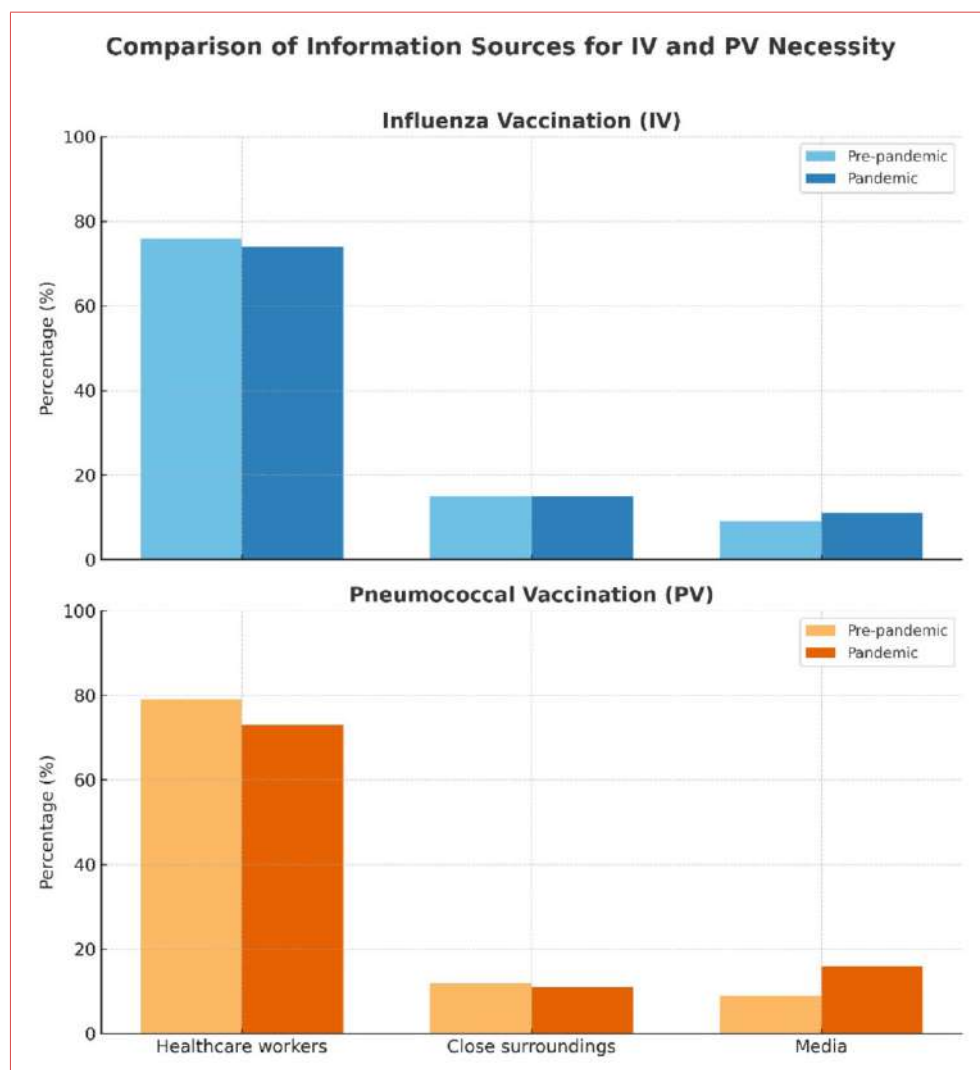


Figure 4. Comparison of first sources of information for influenza and pneumococcal vaccination necessity across pre-pandemic and pandemic periods (p-values: Influenza vaccination $p=0.159$, Pneumococcal vaccination <0.001).

lower routine IV and PV rates. In our sample, no individuals with a diagnosis of T1DM received the IV or PV during the COVID-19 pandemic.

During the pandemic, regression analysis identified several predictors of IV. Older age (67 ± 10 vs. 53 ± 9.5 years; odds ratio [OR] 1.065, 95% confidence interval [CI] 1.023–1.120; $p=0.002$); longer diabetes duration (14 ± 8 vs. 9.9 ± 4.4 years; OR 1.064, 95% CI 1.011–1.126; $p=0.017$); prior IV predicted continued IV (97% vs. 3%; OR 0.011, 95% CI 0.004–0.036; $p=0.001$). History of COVID-19 infection (44% vs. 24%; OR 0.392, 95% CI 0.218–0.707; $p=0.001$) and COVID-19 vaccination (99% vs. 79%; OR 0.078, 95% CI 0.012–0.503; $p=0.007$). For PV, older age (73 ± 7 vs. 56 ± 10 years; OR 1.139, 95% CI 1.069–1.214; $p<0.001$), prior

IV (97% vs. 3%; OR 0.053, 95% CI 0.031–0.090; $p<0.001$), history of COVID-19 infection (57% vs. 26%; OR 0.325, 95% CI 0.137–0.658; $p=0.013$).

DISCUSSION

In addition to its alarming impact on human health, the COVID-19 pandemic has also promoted public awareness of health-protective behaviors, particularly vaccination, clearly reflected in our study findings. Specifically, the heightened awareness of vaccine-related benefits during the pandemic appeared to positively influence IV and PV acceptance among diabetic patients. Although the observed increases in IV and PV uptake were still suboptimal, a measurable improvement was noted during the early pandemic compared to pre-pandemic

Table 3. Factors associated with IV rates before and during the COVID-19 pandemic

Variables	IV in the pre-pandemic period			IV during the pandemic period		
	Vaccinated (n=143)	Non-vaccinated (n=372)	p	Vaccinated (n=210)	Non-vaccinated (n=305)	p
Age, year, mean±SD	70.4±9.9	55.03±9.5	<0.001	67.5±10.1	53.7±9.5	<0.001
Gender n, (%)						
Male	67 (47)	131 (36)		86 (41)	112 (37)	
Female	76 (53)	241 (64)	0.015	124 (59)	193 (63)	0.332
Marital status n, (%)						
Living with family	87(61)	315 (85)		143 (68)	259 (85)	
Living alone	56 (39)	57 (15)	<0.001	67 (32)	46 (15)	<0.001
Education n, (%)						
Illiterate	23 (16)	54 (15)		38 (18)	39 (13)	
Primary school	54 (38)	115 (31)		78 (37)	91 (30)	
Middle school	53 (37)	69 (18)		68 (32)	54 (18)	<0.001
High school	6 (4)	81 (22)	<0.001	16 (8)	71 (23)	
University	7 (5)	53 (14)		10 (5)	50 (16)	
Diabetes duration, years (mean±SS)	14.7±8.2	10.4 ±5.3	<0.001	14±8.1	9.9±4.4	<0.001
Diabetes type n,(%)						
Type 1 DM*	4 (2,8)	32 (8.6)	0.012	0	36(12)	<0.001
Type 2 DM*	143 (97.2)	336 (91.4)		210 (100)	269 (88)	
Comorbidities n, (%)						
Hypertension	130 (91)	256 (69)	<0.001	189 (90)	197 (64)	<0.001
CAD**	92 (64)	85 (23)	<0.001	132 (63)	45 (13)	<0.001
CVD***	10 (7)	2 (0.5)	<0.001	11 (5)	1(0.3)	<0.001
CKD&	45 (32)	40 (11)	<0.001	65 (31)	20 (6)	<0.001
CPD&&	45 (32)	40 (11)	<0.001	68 (32)	17 (5)	<0.001
COVID-19 infection n, (%)	-	-	-	92 (44)	73 (24)	<0.001
COVID-19 vaccination n, (%)	-	-	-	208 (99)	242 (79)	<0.001
Awareness of COVID-19 vaccination and its benefits n, (%)	-	-	-	205 (98)	244 (80)	0.023*
Pre-pandemic PV n, (%)				59 (28)	0	<0.001
Pre-pandemic IV n, (%)	-	-	-	139 (97)	4(3)	<0.001

*DM: Diabetes mellitus, **CAD: Coronary artery disease; ***CVD: Cerebrovascular disease; CKD&: Chronic kidney disease, CPD&&: Chronic pulmonary disease, SD: Standard deviation, IV: Influenza vaccination, PV: Pneumococcal vaccination

levels. However, 46% of study participants remained unaware of the recommended IV and/or PV for diabetics by the end of 2021. Conventional factors affecting IV and PV remained consistent across both periods. Nevertheless, during the pandemic, a history of COVID-19 infection and prior COVID-19

vaccination emerged as significant determinants of routine vaccination uptake.

Previous national studies, conducted before the COVID-19 pandemic, most of which were limited by relatively small

Table 4. Factors associated with pneumococcus vaccination rates before and during the COVID-19 pandemic

Variables	PV in the pre-pandemic period			PV during the pandemic period		
	Vaccinated (n=59)	Non-vaccinated (n=456)	p	Vaccinated (n=95)	Non-vaccinated (n=420)	p
Age, years; mean±SD	70.6±5.1	56.9±10.3	<0.001	73.6±7.6	56±10.1	<0.001
Gender n, (%)						
Male	21(36)	177 (39)		33 (35)	165 (39)	0.410
Female	38 (65)	279 (61)	0.672	62 (65)	255 (61)	
Marital status n, (%)						
Living with family	36(61)	379 (83)		54 (57)	348 (85)	<0.001
Living alone	23 (39)	77 (17)	0.051	41 (43)	72 (15)	
Education n, (%)						
Illiterate	9 (15)	68 (15)		16 (17)	61 (14)	<0.001
Primary school	12 (20)	157 (34)		24 (25)	145 (35)	
Middle school	37 (63)	85 (19)		49 (52)	73 (17)	
High school	0 (0)	87 (19)	<0.001	3 (3)	84 (20)	
University	1 (2)	59 (13)		3 (3)	57 (14)	
Diabetes duration years; mean±SD	17.8±7.6	10.8±5.9	<0.001	15.7±7.5	10.6±5.9	<0.001
Diabet type n,(%)						
Type 1 DM*	0	36(8)	0.025	0	36 (8)	0.003*
Type 2 DM*	59 (100)	420 (92)		95 (100)	384 (92)	
Comorbidities n, (%)						
Hypertension	57 (97)	329 (72)	<0.001	91 (96)	295 (70)	<0.001
CAD**	50 (85)	127 (28)	<0.001	72 (76)	105 (25)	<0.001
CVD***	6 (10)	6 (1)	<0.001	8 (8)	4 (0.9)	<0.001
CKD&	28 (47)	57 (12)	<0.001	39 (41)	46 (11)	<0.001
CPD&&	30 (51)	55 (12)	<0.001	44 (46)	41 (10)	<0.001
COVID-19 infection history n, (%)	-	-	-	54 (57)	111 (26)	<0.001
COVID 19 vaccination n, (%)	-	-	-	95 (100)	355 (85)	<0.001
Awareness of COVID-19 vaccination and their benefits n, (%)	-	-	-	95 (100)	354 (85)	0.016
Pandemic IV n, (%)	-	-	-	92 (97)	118 (28)	<0.001
Pre-pandemic IV n, (%)				76 (80)	67(16)	<0.001

*DM: Diabetes mellitus, CAD: Coronary artery disease, ***CVD: Cerebrovascular disease, CKD&: Chronic kidney disease, CPD&&: Chronic pulmonary disease, IV: Influenza vaccination, PV: Pneumococcal vaccination, SD: Standard deviation

sample sizes, consistently reported low IV and PV rates in diabetic patients, with only minimal annual fluctuations (Table 5).^[3-7] Rates tended to be higher and more variable in studies involving older populations.^[4] In 2013, Satman et al.^[8] published the results of a large-scale epidemiological study (based on data from 2009), which revealed rates of 27% and 9.8% for IV and PV, respectively, among diabetic patients. Eight

years later, a nationwide multicenter survey involving 37 cities, utilizing data from 2017, demonstrated comparable IV and PV rates among diabetic patients.^[9] Our pre-pandemic findings align closely with these observations, confirming persistently low coverage levels. During the pandemic, however, the results of studies conducted in our country were reported to be mixed.^[10-14] Korkmaz et al.,^[10] observed a rise in PV rates, but

Table 5. Studies evaluated the rates of IV and PV among patients with diabetes mellitus

Studies and published years	Data collection years	Age Mean±SD	Number of patients	IV (%)	PV (%)	Period
Satman et al. ^[8]	2009		5682	27	9.8	Pre-pandemic
Apaydin et al. ^[3]	2014–2017	58±11	504	10.1	5	Pre-pandemic
Isık et al. ^[4]	2020	65	293	34.1	9.9	Pre-pandemic
Arslan et al. ^[6]	2016	54	318	14.6	3.8	Pre-pandemic
Sözen et al. ^[7]	2019	57±11	202		14.7	Pre-pandemic
Yeşilova et al. ^[5]	2019	57±10.7	350	26	10.8	Pre-pandemic
Demirci et al. ^[9]	2017		5175	23.6 T1DM* 21.2 T2DM**	8 (T1DM) 7 (T2DM)	Pre-pandemic
Mercan Baspinar et al. ^[12]	2022	59.7±13	280	16.8	17.5	Pandemic
Karagun et al. ^[11]	2021	53±12	424	36.6	34.9	Pandemic
Korkmaz et al. ^[10]	2023	52±17	500	28.2	23.6	Pandemic

*T1DM: Type 1 diabetes mellitus, **T2DM: Type 2 diabetes mellitus, &: Reference number, SD: Standard deviation, IV: Influenza vaccination, PV: Pneumococcal vaccination

no change in IV rates. Karagun et al.^[11] reported higher uptake for both vaccines (34.9% for PV and 36.6% for IV), whereas Mercan Baspinar and Demirci found rates comparable to those of the pre-pandemic period.^[12] All reported high uptake of COVID-19 vaccination (87.4–91.2%), similar to our cohort.^[10,14] Overall, our findings regarding IV and PV fall within the range reported by Karagun et al.^[11] and Korkmaz et al.,^[10] but remain well below the WHO-recommended levels >75% coverage for high-risk populations.^[15]

International data on routine vaccination rates during the pandemic in specific risk populations have shown heterogeneity, with some studies reporting declines and others reporting increases.^[16–20] For example, Breuker et al.^[16] observed a small increase in infection risk awareness among patients with chronic diseases, including 750 people with diabetes, but without a change in willingness to vaccinate. Their reported IV and PV rates (59.7% and 28.4%, respectively) were still higher than ours.^[16–20] Similarly, Sosa Liprandi et al.^[17] found that immunization coverage during the pandemic remained low in cardiometabolic patients, most of whom were diabetics. In contrast, in a different high-risk population (psoriasis), a significant increase was reported, with a lifetime PV prevalence rising from 16.0% to 41.5% and IV prevalence from 50.5% to 66.2%.^[18] Such variability in routine vaccination rates among high-risk patients likely reflected differences in geography, healthcare access, and sociocultural attitudes.

Concerted efforts from governmental institutions and the media largely influenced the elevated COVID-19 vaccination rates found among our patients. However, during the

pandemic, similar to pre-pandemic study findings, the primary source of information for both IV and PV remained healthcare workers, reaffirming their pivotal role in patient education and vaccine advocacy.^[8,10,11,16–18] Before the pandemic, a lack of sufficient awareness about vaccination was identified as a significant issue, contributing to low vaccination rates.^[4–6] In some samples, 18.9–47.8% of diabetic patients reported awareness of IV/PV recommendations, with much lower figures for PV.^[4,6,21] In our data, awareness increased from 32% to 54% for IV and 15% to 28% for PV during the pandemic, paralleling increases in vaccine uptake. Unlike pre-pandemic studies where awareness exceeded vaccination, during the pandemic, diabetic patients showed more actionable awareness. However, despite this improvement in vaccination awareness during the pandemic, the lack of knowledge about the necessity of IV and PV persisted as the most frequently cited reason for non-vaccination in both periods, echoing findings from previous studies.^[4,5,8,10,16,17,22]

The pandemic reshaped attitudes toward routine vaccinations. While many patients maintained a positive attitude, some previously hesitant individuals became more accepting, as reported in the literature.^[16,20,23] In our study, a small subgroup, however, shifted from a positive to a negative stance, even among some who had received IV and/or COVID-19 vaccines, indicating residual doubt. Among our aware subgroup, explicit anti-vaccine sentiment was <1%, markedly lower than the 8.7% reported by Karagun et al.^[11] Reasons for vaccine refusal also evolved in our patients; in pre-pandemic, negligence and indecision were predominant, while safety concerns became more prominent during the pandemic. This shift in

refusal reasons mirrors the patterns reported in other studies and highlights the need for sustained targeted educational strategies to address the misinformation and prevent the spread of conspiracy beliefs.^[13,16] Consistent with prior literature, we found that IV and PV uptakes were influenced by age, diabetes type and duration, education level, living arrangements, and comorbidities.^[3,5,10,16,17]

Despite the generally positive effect of education level on vaccination uptake, our study revealed an unexpected finding: individuals with higher education attainment had significantly lower rates of IV and PV.^[11,24] Most of these participants were younger patients with T1DM. Thus, the lower IV and PV rates associated with higher education level were driven partly by the subset of highly educated and partly younger T1DM patients. Early-pandemic debates on vaccine efficacy and safety in autoimmune conditions likely influenced vaccine avoidance behaviors, including routine vaccinations, among patients with T1DM in our cohort. Given the small T1DM subgroup, these results should be interpreted as preliminary rather than definitive. Nevertheless, the observed gap between educational attainment and certain preventive health behaviors highlights a critical gap, suggesting that general education alone may be insufficient and that vaccine-specific health literacy is essential. Although early-pandemic debates on vaccine efficacy and safety in autoimmune conditions likely led to the avoidance of all vaccinations, including routine ones, among these T1DM patients, this finding emphasizes that general education alone is insufficient; vaccine-specific health literacy is critical. Supporting this, Guclu et al.^[25] linked greater “disease prevention health literacy” with higher IV/PV rates within the general population, and Satman et al.^[8] demonstrated that a 4-month physician-led education initiative increased IV and PV uptake by 2.5–4-fold in the pre-pandemic period. In our study, 81% of previously vaccine-unaware diabetic patients expressed willingness to vaccinate after receiving physician advice, illustrating once more the leverage of direct healthcare provider communication and highlighting the need for system-level interventions to “nudge” patients toward preventive action.

In multivariate analysis, older age, longer diabetes duration, prior IV vaccination, history of COVID-19, and COVID-19 vaccination were identified as independent predictors of IV during the pandemic.^[5,8,10] For PV, older age and a history of COVID-19 infection emerged as independent factors. These findings suggested that personal experience with COVID-19 may influence engagement in preventive health behaviors. Moreover, previous positive attitudes toward vaccination may reinforce acceptance of other vaccines, consistent with the “spill-over” effect described in the literature.^[23,26]

Limitation

This study has several limitations. The single-center design may limit generalizability. Partial reliance on self-reported vaccination status introduces potential recall bias, although electronic health records were used for verification whenever possible. Residual confounding was possible despite the multivariable adjustment. Despite these limitations, the within-subject comparison provides valuable insight into temporal changes in vaccination behavior among diabetic patients.

CONCLUSION

The COVID-19 pandemic catalyzed increased awareness and uptake of IV and PV among diabetic patients; however, coverage remains below international targets. Older age, prior vaccination behavior, and personal experience with COVID-19 were key facilitators of vaccine acceptance. To close the persistent coverage gap, multifaceted strategies are needed to improve access and reduce vaccine refusal by combining physician-led education, increased patient vaccine accountability, proactive risk communication, and systems-level interventions.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital Ethics Committee (No: E-48670771–514.99, Date: 03/10/2022).

Informed Consent: Written informed consent was obtained from all participants. Participant confidentiality and data privacy were strictly maintained; all personal identifiers were removed from the dataset, and data were stored securely with access limited to the research team.

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Is Prophylactic Fixation Necessary After Extended Curettage and Cementation of Lower Extremity Cartilage Tumors? A Retrospective Analysis of Fracture Risk and Functional Outcomes

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ABSTRACT

Objective: Extended intralesional curettage followed by cementation is widely accepted for the treatment of low-grade cartilaginous tumors of the long bones. However, the necessity of prophylactic internal fixation to prevent post-operative fractures remains controversial. The aim of this study is to assess fracture risk and functional outcomes in patients undergoing extended curettage and cementation for lower extremity cartilaginous tumors without prophylactic fixation.

Materials and Methods: This retrospective study included 98 patients with lower extremity cartilaginous tumors treated with extended curettage and polymethylmethacrylate cementation without prophylactic fixation between 1996 and 2024. Fracture incidence, oncological outcomes, and functional results assessed by Musculoskeletal Tumor Society, Harris Hip Score, Knee Society Score, and American Orthopaedic Foot and Ankle Society Score were analyzed over a mean follow-up of 56 months.

Results: Post-operative fractures occurred in five patients (5%), four of which were incomplete and managed successfully with conservative treatment or limited fixation. All fractures achieved union without long-term functional compromise. No local recurrence, metastasis, or infection was observed. At final follow-up, all patients were classified as having no evidence of disease. Functional outcomes were excellent, with mean scores exceeding 90% across all scoring systems.

Conclusion: Extended curettage and cementation without prophylactic fixation provides oncologically safe treatment, acceptable fracture risk, and excellent functional outcomes for selected lower extremity cartilaginous tumors. Avoiding routine fixation eliminates implant-related complications and imaging artifacts while preserving mechanical stability when meticulous surgical technique and controlled post-operative rehabilitation are applied.

Keywords: Bone cements, cartilage neoplasms, curettage

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INTRODUCTION

Cartilaginous tumors constitute a distinct subgroup of bone lesions in orthopedic oncology, characterized by unique diagnostic challenges and tailored therapeutic strategies. Extended intralesional procedures such as curettage followed by cementation are widely employed to achieve local tumor control while preserving joint integrity and maximizing post-operative function. Despite their efficacy in local tumor control, these procedures inherently create a structural defect in the bone, which may predispose patients to post-operative complications, particularly increasing the fracture risk.^[1]

Although previous studies have demonstrated the oncological safety of extended curettage and cementation for these lesions, evidence regarding mechanical stability and functional outcomes in the absence of prophylactic fixation remains limited. Factors such as lesion size and anatomical location play a critical role in determining the risk of local recurrence and may also influence biomechanical integrity; therefore, fracture risk should be considered as a distinct endpoint.^[2] Moreover, even relatively small lesions have the potential to compromise structural stability, depending on their position within the bone.^[3]

The primary objective of this study is to assess fracture risk and functional outcomes in patients undergoing extended curettage and cementation for lower extremity cartilaginous tumors without prophylactic fixation, providing evidence to inform surgical decision-making and optimize patient management.

MATERIALS AND METHODS

Patient Cohort

A retrospective institutional database review was conducted to identify patients managed for lower extremity cartilaginous tumors at our tertiary musculoskeletal oncology center between 1996 and 2024. Inclusion was restricted to individuals who underwent extended intralesional curettage and cementation without concomitant prophylactic internal fixation. To maintain cohort homogeneity, exclusion criteria comprised a follow-up duration of <24 months, the utilization of local adjuvants other than polymethylmethacrylate (PMMA), and the presence of multicentric lesions.

The study was conducted in accordance with institutional guidelines, and written informed consent for the use of clinical data for research purposes was obtained from all participants at hospital admission. This study was conducted in full compliance with the principles of the Declaration of Helsinki. The research protocol was approved by the Institutional Ethics Committee of Acibadem Mehmet Ali Aydinlar University (date/number: January 08, 2026/2026-01/11).

Surgical Technique and Post-operative Care

Surgical planning was tailored individually for each patient based on their clinical presentation and comprehensive pre-operative imaging, with particular attention to features indicative of malignancy. All cases were reviewed and discussed in a multidisciplinary tumor board to establish an evidence-based operative strategy. All patients underwent intralesional extended curettage and cementation without plate augmentation. All tissue specimens were examined and verified by an experienced musculoskeletal pathologist to ensure diagnostic accuracy. All surgical procedures were performed by the senior author (Prof. Özger), providing uniformity in operative technique and intraoperative decision-making. No patient received neoadjuvant or adjuvant chemotherapy or radiotherapy.

All surgical procedures were performed under general anesthesia. The tumor was precisely localized preoperatively using high-resolution imaging studies, including magnetic resonance imaging (MRI), to delineate its full extent. Based on these findings, a patient-specific incision was planned and executed to provide optimal exposure while minimizing soft-tissue disruption or contamination. A targeted corticotomy was then performed using a high-speed micromotor system (e.g., Midas Rex Legend Triton, Medtronic, Dublin, Ireland), ensuring preservation of surrounding bone and soft-tissue structures. Extended curettage was carried out meticulously, addressing both the intramedullary space and the inner surface of the excised cortical window with a high-speed burr to remove microscopic residual tumor tissue. Intraoperative fluoroscopy was employed to confirm the adequacy of tumor removal and to guide the subsequent steps. Once complete, the cavity was filled with high-viscosity PMMA cement (Versabond®, Smith and Nephew, UK) as a local adjuvant. In our surgical practice, we extend cementation beyond the tumor cavity into the intramedullary space, thereby increasing the cement-filled volume, improving load distribution and the overall mechanical stability of the bone.

The cortical window was repositioned carefully to restore anatomical continuity and facilitate osteointegration, without the use of additional fixation. Hemostasis was ensured, and meticulous soft-tissue closure was performed to optimize post-operative healing.

Although PMMA cement generally provides mechanical stability, rotational movements were strictly avoided until cortical window integration and sufficient radiological healing were achieved, in order to prevent torsional stresses on the bone. Post-operative care followed a structured rehabilitation program patients began with bedside sitting, then assisted ambulation with walkers or crutches. Weight bearing advanced

from toe-touch to partial, and finally full load after radiological evidence of bone healing.

Follow-up and Outcome Assessment

Patients were monitored according to a structured follow-up protocol, which included monthly imaging for the first 3 months for cortical window integration, every 3 months for the subsequent 2 years, every 6 months for the following 3 years, and annual evaluations up to 10 years postoperatively. Functional outcomes were systematically assessed using the Musculoskeletal Tumor Society (MSTS) scoring system.^[4] In addition, the Harris Hip Score (HHS),^[5] Knee Society Score (KSS),^[6] and the American Orthopaedic Foot and Ankle Society Score (AOFAS)^[7] were applied to assess hip, knee, and ankle functions, respectively. Oncological outcomes were classified in accordance with the International Society of Limb Salvage (ISOLS) criteria.^[8]

The primary endpoint of the study was to evaluate the occurrence of post-operative fractures prior to complete osseous consolidation, confirmed through both clinical evaluation and radiographic assessment. Hence, the incidence of post-operative fractures and their respective management strategies were meticulously documented throughout the follow-up period.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences software (version 25.0, IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as means with ranges for continuous variables and as frequencies with percentages for categorical variables. Patients who developed post-operative fractures were compared with those without fractures in terms of tumor volume using the Mann–Whitney U test, while the association between fracture occurrence and tumor location was analyzed using the Chi-square test. $P<0.05$ was considered as statistically significant.

RESULTS

The study cohort included 98 patients (76 females and 22 males) with a mean age of 42 years (range, 13–73) at the time of surgery. Histopathological diagnoses consisted of atypical cartilaginous tumors (52%; $n=51$), low-grade chondrosarcomas (36%; $n=35$), and enchondromas (12%; $n=12$). The mean tumor volume was 30 cm³ (range, 6–68). Regarding anatomical distribution, lesions were predominantly located in the distal femur ($n=43$), followed by the proximal femur ($n=22$), femoral diaphysis ($n=20$), proximal tibia ($n=11$), and tibial diaphysis ($n=2$). The mean post-operative follow-up was 56 months (range, 26–240). Post-operative fractures were observed in five patients. In a patient with a femoral head lesion treated with extended curettage and cementation, an incomplete

fracture developed at post-operative week 7 due to rotational stress, despite prescribed activity restrictions, and was subsequently stabilized with cannulated screw fixation. Two additional patients with distal femoral metaphyseal lesions, along with one patient with a femoral diaphyseal lesion, sustained incomplete fractures through the cortical window following minor rotational trauma in the third post-operative month. Conservative management with restricted weight-bearing ultimately resulted in successful bone healing (Fig. 1). In another patient with an enchondroma in the distal femoral diaphyseal-metaphyseal region, a displaced femoral fracture occurred 1 month postoperatively after a low-energy fall and was treated with plate-and-screw osteosynthesis (Fig. 2). Radiographic bone union was achieved in all cases, with no subsequent complications.

Throughout follow-up, no cases of local recurrence or distant metastasis were identified. According to the ISOLS criteria, all patients were classified as no evidence of disease at their final evaluation. In addition, no superficial or deep infections, nor wound-related complications, were encountered. The functional outcomes are summarized in Table 1.

Comparative analysis revealed no statistically significant differences in tumor volume between patients with and without post-operative fractures ($p>0.05$). In addition, fracture occurrence was not significantly associated with tumor location within the lower extremity ($p>0.05$).

DISCUSSION

Our findings demonstrate that extended intralesional curettage followed by cementation, even without prophylactic internal fixation, provides excellent functional outcomes and acceptable fracture risk in lower extremity cartilaginous tumors. The absence of plate augmentation did not compromise mechanical stability or patient-reported function, aligning with the fracture incidence and oncologic safety rates previously reported in the literature.^[9-13] In our series, only five post-operative fractures were observed (5%), a frequency comparable to those in studies that included

Table 1. Functional outcomes of the patients (n=98)

Outcome measure	Mean	Range
MSTS (%)	93	(83–96)
HHS	95	(93–98)
KSS	93	(90–98)
AOFAS	96	(94–100)

MSTS: Musculoskeletal tumor society; HHS: Harris hip score; KSS: Knee society score; AOFAS; American orthopaedic foot and ankle society score.



Figure 1. (a, b) Contrast-enhanced sagittal and axial magnetic resonance (MR) images of a 40-year-old female patient demonstrating an intramedullary cartilaginous lesion in the distal femur. (c, d) Early post-operative anteroposterior and lateral radiographs obtained following extended curettage and cementation. (e, f) Sagittal T1- and T2-weighted MR sequences at 3 months postoperatively, revealing a fissure line (white arrow) extending to the cortical window with surrounding bone marrow edema.



Figure 2. (a, b) Contrast-enhanced sagittal and axial magnetic resonance images of a 23-year-old female patient demonstrating an intramedullary cartilaginous tumor in the distal femur. (c, d) Early post-operative anteroposterior and lateral radiographs of the same patient. (e) Three-dimensional computed tomography image obtained at 1 month postoperatively following a fall, showing a fracture at the proximal margin of the cement (red arrow). (f) Anteroposterior (AP) radiograph at 4 years postoperatively after minimally invasive plate osteosynthesis. (g) AP radiograph of the femur after removal of the implants due to irritation of the soft tissues

patients treated with prophylactic osteosynthesis.^[9,10,14] This reinforces that prophylactic plating may not be necessary when meticulous curettage and optimized cementation techniques are employed.

A pivotal technical nuance of our approach involves extending the cement mantle beyond the lesion into adjacent intramedullary segments, thereby increasing the effective cement volume and optimizing load distribution across a broader surface area. This technique appears to enhance the biomechanical stiffness of the bone and may compensate for the absence of fixation hardware, particularly in diaphyseal or metaphyseal locations where torsional forces predominate. Previous biomechanical studies have similarly suggested that the principal determinants of fracture risk are the residual cortical thickness and cement volume, rather than the presence of fixation plates.^[15] Accordingly, our strategy of extended cementation likely contributed to the low rate of mechanical complications observed.

The reported fracture rates after curettage and cementation in the literature vary between 3% and 10%, depending on lesion size, cortical involvement, and post-operative rehabilitation.^[9,10,14] Krebbekx et al.^[9] identified lesion size greater than 38 mm and male sex as independent predictors of fracture, while Errani et al.^[2] noted that cortical thinning was a major factor influencing both local recurrence and mechanical failure. Our findings are consistent with these reports; however, given that none of our patients with larger lesions required secondary fixation due to instability, we believe that a carefully controlled mobilization protocol and rotational movement restriction in the early post-operative period play an essential role in reducing fracture risk. Specifically, torsional stresses through the cortical window may precipitate incomplete fractures, as observed in a small number of our cases, but conservative management with weight-bearing modification resulted in complete union without functional compromise.

Importantly, avoiding prophylactic metallic implants offers substantial advantages for post-operative imaging surveillance. Metallic fixation devices create susceptibility and beam-hardening artefacts on MRI and computed tomography, which can significantly obscure the evaluation of cortical integrity and potential local recurrence.^[16-19] Despite recent advances in metal artefact reduction sequences, these technologies are not universally accessible and remain time-consuming.^[16-19] By obviating the need for metallic hardware, our strategy facilitates artifact-free imaging, thereby enhancing the diagnostic sensitivity for early local recurrence and providing a more precise assessment of osseous consolidation. This represents a distinct advantage in

managing low-grade cartilaginous lesions that require long-term surveillance.

Functional outcomes in our series were uniformly excellent, with mean MSTs, HHS, KSS, and AOFAS scores exceeding 90%. These findings are consistent with prior reports of superior post-operative function after intralesional procedures compared to wide resections.^[11-13] However, there remains a notable paucity of studies directly comparing functional outcomes between fixation and non-fixation groups. The literature includes over 2,000 cases treated with intralesional curettage since 2015, yet only a limited subset provides validated MSTs or Toronto Extremity Salvage Score (TESS) data.^[11-16,20-23] Our results, therefore, contribute novel evidence supporting that functional recovery can be excellent even in the absence of plate fixation, provided that mechanical stabilization through extended cementation and structured rehabilitation protocols is achieved. Future prospective comparative studies are warranted to confirm these findings and further elucidate the biomechanical and functional benefits of avoiding unnecessary fixation.

In conclusion, our experience supports that extended curettage and cementation without prophylactic fixation is both oncologically safe and mechanically sound for the management of lower extremity cartilaginous tumors. When cementation is extended beyond the tumor cavity to increase load distribution and post-operative mobilization is appropriately restricted, fracture risk remains within the range reported in the literature. Moreover, the elimination of metal artefacts during follow-up imaging significantly enhances surveillance accuracy. Considering these mechanical, functional, and imaging advantages, we advocate for fixation-free extended curettage and cementation as a sufficient and effective strategy in appropriately selected patients.

Limitations

This study has several limitations inherent to its retrospective design. The relatively small number of post-operative fracture events limits the statistical power to identify specific predictive factors. Moreover, the absence of a control group treated with prophylactic fixation precludes direct biomechanical comparison between fixation and non-fixation strategies. Although a single-surgeon series provides uniformity, it may introduce selection bias.

Finally, larger multicenter cohorts would provide greater external validity and strengthen the generalizability of our findings.

CONCLUSION

Extended curettage and cementation without plate augmentation for lower extremity cartilage tumors,

supported by meticulous surgical technique and carefully supervised post-operative rehabilitation, minimize fracture risk, ensure excellent functional outcomes, and optimize radiologic surveillance while avoiding implant-related complications.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Acibadem Mehmet Ali Aydinlar University Ethics Committee (No: 2026/2026-01/11, Date: 08/01/2026).

Informed Consent: Written informed consent for the use of clinical data for research purposes was obtained from all participants at hospital admission.

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Association Between Hoffa Fat Pad Morphology And Magnetic Resonance Imaging-Based Posterior Horn Meniscal Grade: A Retrospective Magnetic Resonance Imaging Study

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ABSTRACT

Objective: The objective of the study was to evaluate the association between Hoffa's fat pad morphology and Magnetic resonance imaging (MRI)-based posterior horn meniscal grade and to determine whether this association remained after adjustment for age, sex, and body mass index (BMI).

Materials and Methods: In this retrospective cross-sectional MRI study, 144 adults were intentionally selected using a grade-balanced sampling strategy, with 36 patients assigned to each MRI-based posterior horn meniscal grade (Grades 0–3). Hoffa fat pad thickness and sagittal cross-sectional area (CSA) were measured. Spearman's analysis was used to examine correlations. Group differences were tested by Kruskal–Wallis and Dunn's multiple comparison tests. Ordinal logistic regression was performed to identify factors independently associated with higher MRI-based posterior horn meniscal grade after adjustment for age, sex, and BMI.

Results: Hoffa's fat pad thickness and CSA decreased progressively with increasing meniscal grade. Both parameters showed significant negative correlations with grade severity, stronger for CSA ($r=-0.483$, $p=0.001$) than thickness ($r=-0.254$, $p=0.002$). Age showed a weak positive correlation with MRI grade ($r=0.191$, $p=0.022$); however, this association was not retained after multivariable adjustment. Hoffa's fat pad CSA (odds ratio [OR]=0.985, 95% confidence interval [CI]: 0.980–0.990, $p<0.001$) and male sex (OR=4.323, 95% CI: 1.921–9.728, $p<0.001$) were independently associated with higher MRI-based posterior horn meniscal grade. The proportional odds assumption was satisfied. No statistically significant differences in Hoffa fat pad morphology were observed between isolated medial and combined medial+lateral posterior horn involvement.

Conclusion: Hoffa fat pad CSA was inversely associated with MRI-based posterior horn meniscal grade and may represent an imaging feature associated with structural meniscal abnormalities.

Keywords: Degeneration, Infrapatellar fat pad, Knee joint, Magnetic resonance imaging, Menisci

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INTRODUCTION

The menisci play an important role in load transmission, shock absorption, and joint stability in the knee. Degenerative meniscal changes are frequent, especially with increasing age, and are thought to be a major cause of knee pain and osteoarthritis.^[1,2] Magnetic resonance imaging (MRI) is considered the gold standard for non-invasive assessment of meniscal lesions, providing information on both morphological and signal changes.^[3]

The Infrapatellar fat pad (IFP), also known as Hoffa's fat pad, is an intracapsular and extrasynovial structure in the anterior compartment of the knee. In addition to mechanical function, it is being recognized as a metabolically active tissue in inflammatory and degenerative conditions of the knee joint.^[4,5] Hoffa fat pad is known to secrete several cytokines and adipokines that might be involved in cartilage degradation and synovial inflammation.^[6]

Recent studies have reported that the Hoffa fat pad is modified structurally (thickness and cross-sectional area [CSA]) in knee joint internal derangements such as osteoarthritis, meniscal disorders, and early degenerative changes, including chondromalacia.^[7-9] However, the correlation between Hoffa fat pad morphology and the degree of meniscal degeneration is not fully understood.

Meniscal degeneration is commonly graded using MRI-based classification systems, reflecting progressive structural deterioration. To our knowledge, prior studies have mainly addressed the meniscal tears or osteoarthritis, and limited data exist regarding the association between Hoffa fat pad morphology and MRI-based posterior horn meniscal grades.^[10-14] Furthermore, it is still not defined whether demographic or clinical characteristics, including age, sex, and body mass index (BMI), can affect the association.

Therefore, this study aimed to investigate the association between Hoffa fat pad morphology, including sagittal thickness and CSA, and MRI-based posterior horn meniscal grade. In addition, we examined whether these MRI-derived morphological parameters were independently associated with higher MRI-based posterior horn meniscal grades after adjustment for age, sex, and BMI.

MATERIALS AND METHODS

Study Design and Population

This retrospective cross-sectional study was approved by the Gaziantep University Ethics Committee (Decision No: 2026/139; February 18, 2026), and the requirement for informed consent was waived because of the retrospective study design. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consecutive knee MRI examinations performed between September 01, 2022, and January 30, 2026 were identified from the institutional Picture Archiving and Communication System. A total of 256 consecutive knee MRI examinations were initially reviewed.

Inclusion criteria were as follows: (1) available knee MRI images with good image quality, and (2) patients were adults.

Exclusion criteria were: (1) Previous knee surgery, (2) acute knee injury, (3) inflammatory arthropathy, (4) chondromalacia or significant cartilage degeneration, (5) severe osteoarthritis preventing a reliable meniscal reading, (6) tumor or tumor-similar lesion affecting the knee joint, or (7) inadequate image quality.

After application of the predefined inclusion and exclusion criteria, eligible examinations were categorized according to MRI-based posterior horn meniscal grade (Grades 0–3). To facilitate balanced comparisons across degeneration grades and minimize class imbalance during statistical analyses, a grade-balanced sampling strategy was adopted. Specifically, 36 examinations were randomly selected from each MRI grade whenever more than 36 eligible examinations were available, resulting in a final study cohort of 144 patients (36 patients per grade) (Fig. 1).

Because the study intentionally used a grade-balanced sampling strategy rather than the natural distribution of MRI grades within the source population, the ordinal

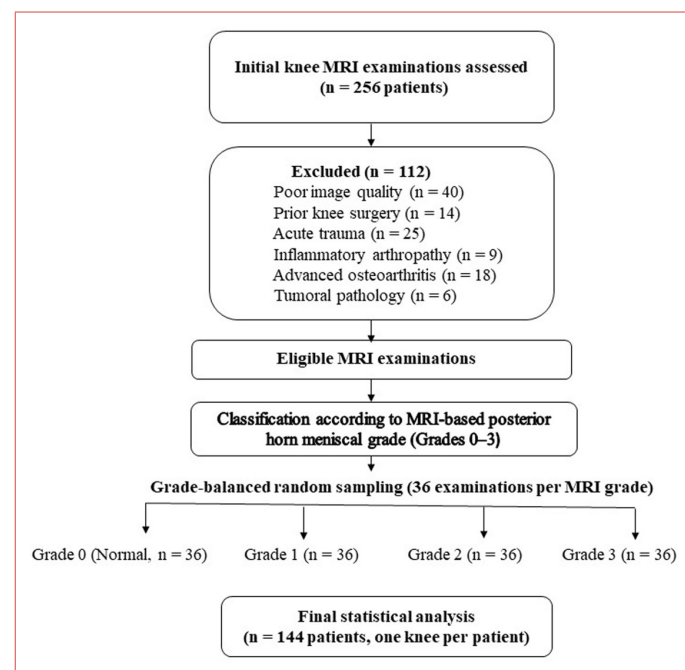


Figure 1. Flowchart of the study design and patient selection process.

logistic regression analyses were designed to evaluate adjusted associations between imaging variables and MRI-based posterior horn meniscal grade within the selected cohort. Therefore, the estimated odds ratios (ORs) should be interpreted as measures of association rather than estimates of population-level risk or predictive performance.

For patients who underwent bilateral knee MRI examinations, only one knee per patient was included to avoid within-subject correlation. When both knees were available, the knee with the higher MRI-based posterior horn meniscal grade was selected for analysis. If both knees demonstrated the same grade, one knee was randomly selected.

MRI Protocol

All MRI examinations were performed using a 1.5-Tesla MRI scanner (Magnetom Aera, Siemens, Germany) with a dedicated knee coil. Patients were positioned supine with the knee in full extension and the patella centered in the coil. No intravenous contrast was administered.

The imaging protocol included the following sequences:

Sagittal proton density (PD) fat-suppressed sequence: Slice thickness 3 mm, interslice gap 0.5 mm, field of view (FOV) 160×160 mm, matrix 320×320, repetition time (TR) 3000 ms, echo time (TE) 30 ms.

Sagittal T1-weighted sequence: Slice thickness 3 mm, FOV 160×160 mm, matrix 320×320, TR 500 ms, TE 10 ms.

Coronal PD fat-suppressed sequence: Slice thickness 3 mm, FOV 160×160 mm, matrix 320×320, TR 2850 ms, TE 30 ms.

Axial PD fat-suppressed sequence: slice thickness 3 mm, FOV 160×160 mm, matrix 320×320, TR 3000 ms, TE 35 ms.

All sequences were acquired with a FOV sufficient to cover the entire knee joint, including the patellofemoral and tibiofemoral

compartments. Studies with gross motion artefacts or with poor meniscal or Hoffa fat pad visibility were excluded. For quantitative analysis, measurements were performed on sagittal PD fat-suppressed and sagittal T1-weighted images, while coronal and axial PD fat-suppressed sequences were used for complementary anatomical evaluation and confirmation of associated findings.

Image Analysis

All MRI examinations were independently reviewed by a radiologist with 7 years of musculoskeletal imaging experience, blinded to patients' clinical and demographic information.

Meniscal Evaluation

To avoid confounding effects from varying patterns across different anatomical regions, meniscal degeneration was assessed selectively within the posterior horn of the menisci, where mechanical load transmission is most prominent during joint loading. Degeneration was graded on MRI according to standard imaging criteria:^[3,15]

- Grade 0: Normal meniscus structure in the posterior horn
- Grade 1: Focal intrameniscal signal confined to the posterior horn
- Grade 2: Linear intrameniscal signal confined to the posterior horn
- Grade 3: Linear signal extending to at least one articular surface of the posterior horn, consistent with MRI findings of a meniscal tear (Fig. 2).

When different MRI grades were present in the medial and lateral posterior horns, the higher grade was considered the index MRI-based posterior horn meniscal grade for statistical analysis.

Posterior horn involvement was additionally classified as isolated medial involvement or combined medial and lateral



Figure 2. Proton density (PD) weighted sagittal images demonstrating meniscal grading in the posterior horn of the medial meniscus: (a) normal, (b) grade 1, (c) grade 2, and (d) grade 3. The relevant findings are indicated by yellow arrows.

involvement. No patient demonstrated isolated lateral posterior horn abnormalities.

Hoffa Fat Pad Measurements

Hoffa's fat pad was assessed on sagittal MRI images, in accordance with previously published criteria.^[9,10,16-18] Measurements included:

Thickness (mm)

The maximal sagittal thickness of the IFP was measured at the level of its greatest anteroposterior dimension, using a line drawn perpendicular to the patellar tendon between the anterior and posterior margins (Fig. 3).

CSA (mm²)

The CSA of the IFP was measured on the sagittal slice demonstrating its largest extent by manually tracing its margins (Fig. 4).

All measurements were performed twice by the same radiologist at a 2-week interval to ensure consistency and assess intraobserver reproducibility, demonstrating good to excellent reliability (intraclass correlation coefficients (ICC)=0.929 for sagittal CSA and 0.947 for sagittal thickness).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 20 software. Normality

of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean±standard deviation for normally distributed data and as median (interquartile range) for non-normally distributed data.

Comparisons among MRI grade groups were performed using the Kruskal–Wallis test, followed by Dunn's *post hoc* test with Bonferroni correction. Associations between Hoffa fat pad measurements and MRI-based posterior horn meniscal grade were evaluated using Spearman's rank correlation analysis. Comparisons between isolated medial and combined medial plus lateral posterior horn involvement were performed using the Mann–Whitney U test.

Univariable ordinal logistic regression analyses were first performed to calculate crude ORs for each independent variable. Subsequently, a multivariable ordinal logistic regression model including age, sex, BMI, Hoffa fat pad thickness, and Hoffa fat pad CSA was constructed to identify variables independently associated with higher MRI-based posterior horn meniscal grade. Adjusted ORs with 95% confidence intervals (CIs) were reported.

Because the study used an intentionally grade-balanced sampling strategy, the regression-derived ORs were interpreted as measures of adjusted association within the selected cohort rather than estimates of population-level risk or predictive performance.



Figure 3. T1-weighted sagittal image illustrating measurement of Hoffa's fat pad thickness, indicated by a yellow line.



Figure 4. T1-weighted sagittal image illustrating measurement of Hoffa's fat pad cross-sectional area, indicated by a yellow shaded region.

The proportional odds assumption was evaluated using the Test of Parallel Lines. Overall model fit was assessed using Pearson and Deviance goodness-of-fit statistics, together with Cox and Snell, Nagelkerke, and McFadden pseudo-R² indices. Multicollinearity among independent variables was assessed using variance inflation factors, and no evidence of problematic multicollinearity was identified.

A two-sided $p<0.05$ was considered statistically significant.

RESULTS

The final study cohort comprised 144 patients (78 women and 66 men) with a mean age of 45.6 ± 13.8 years. According to the study design, 36 patients were included in each MRI-based posterior horn meniscal grade (Grades 0–3). Age did not differ significantly across groups ($p=0.064$), whereas sex distribution ($p=0.974$) and BMI ($p=0.158$) did not differ significantly (Table 1).

Both Hoffa fat pad thickness and sagittal CSA progressively decreased with increasing MRI-based posterior horn meniscal grade (Table 2).

The median Hoffa fat pad thickness was significantly lower in higher MRI grades ($p=0.020$). Similarly, sagittal CSA demonstrated a progressive reduction across MRI grades and showed a stronger association with MRI-based posterior horn meniscal grade ($p=0.001$).

Post hoc analyses demonstrated that the most pronounced differences were observed between Grade 0 and Grades 2–3, whereas adjacent MRI grades showed smaller differences.

Spearman correlation analysis demonstrated a significant inverse correlation between Hoffa fat pad thickness and MRI-based posterior horn meniscal grade ($r=-0.254$, $p=0.002$). An even stronger inverse correlation was observed for Hoffa fat pad CSA ($r=-0.483$, $p<0.001$).

Age demonstrated a weak positive correlation with MRI-based posterior horn meniscal grade ($r=0.191$, $p=0.022$) (Table 3). BMI was not significantly correlated with MRI grade ($p>0.05$).

Univariable ordinal logistic regression analyses demonstrated that lower Hoffa fat pad thickness (OR=0.812, 95% CI: 0.710–0.930, $p=0.002$), lower Hoffa fat pad CSA (OR=0.989, 95% CI: 0.986–0.993, $p<0.001$), and increasing age (OR=1.035, 95% CI: 1.004–1.066, $p=0.025$) were significantly associated with higher MRI-based posterior horn meniscal grade. BMI (OR=1.049, 95% CI: 0.957–1.150, $p=0.305$) and sex (male vs. female: OR=1.093, 95% CI: 0.609–1.965, $p=0.765$) were not significantly associated with MRI grade in the univariable analyses (Table 4).

After adjustment for age, sex, BMI, Hoffa fat pad thickness, and Hoffa fat pad CSA, only lower Hoffa fat pad CSA (adjusted OR=0.985, 95% CI: 0.980–0.990, $p<0.001$) and male sex (adjusted OR=4.323, 95% CI: 1.921–9.728, $p<0.001$) remained independently associated with higher MRI-based posterior horn meniscal grade, whereas Hoffa fat pad thickness, age, and BMI were no longer independently associated (Table 4).

The multivariable ordinal logistic regression model demonstrated adequate overall fit (Likelihood Ratio $\chi^2=53.037$, $p<0.001$). Goodness-of-fit statistics indicated satisfactory agreement between observed and expected values (Pearson $\chi^2=402.496$, $p=0.767$; Deviance $\chi^2=346.216$, $p=0.998$). The proportional odds assumption was satisfied (Test of Parallel Lines, $p=0.754$). The model demonstrated moderate explanatory performance (Nagelkerke $R^2=0.329$, Cox and Snell $R^2=0.308$, McFadden $R^2=0.133$).

Among patients with posterior horn abnormalities, 12 patients demonstrated combined medial and lateral posterior horn involvement, whereas the remaining patients showed isolated medial posterior horn involvement.

No significant differences in Hoffa fat pad thickness or CSA were observed between patients with isolated medial posterior horn involvement and those with combined medial and lateral posterior horn involvement (Table 5). However, the combined involvement group was small and consisted only of patients

Table 1. Demographic characteristics according to posterior horn meniscal grade

Characteristic	Grade 0 (n=36)	Grade 1 (n=36)	Grade 2 (n=36)	Grade 3 (n=36)	p
Age (years), mean±SD	35.69±8.8	39.61±10.5	41.53±7.8	41.11±11.6	0.064
Sex (Male/Female), n	18/18	17/19	16/20	17/19	0.974
BMI (kg/m ²), mean±SD	25.06±2.6	25.05±2.9	26.78±3.4	25.33±3.4	0.136
Side (Right/Left), n	13/23	21/15	16/20	18/18	0.285
Meniscus involvement (Medial / Medial+Lateral), n	36/0	36/0	32/4	28/8	0.001*

Data are presented as mean±standard deviation for continuous variables and number (n) for categorical variables. p-values were calculated using the Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables. Post-hoc comparisons were performed using Dunn's test when appropriate. * $p<0.05$ considered statistically significant

Table 2. Hoffa fat pad thickness and cross-sectional area according to meniscal grade

Grade	Thickness (mm), median (IQR)	Cross-sectional area (mm ²), median (IQR)	p*
0	21.75 (20-23) ^a	618.75 (558.5-679.75) ^a	0.020/0.001
1	21.03 (20-22) ^a	561.53 (499.25-624) ^b	
2	20.33 (19-22) ^{ab}	513.72 (457.5-561) ^c	
3	20.25 (19-21.75) ^b	500.03 (448.25-545.5) ^c	

Values are expressed as median (interquartile range). Overall differences between groups were assessed using the Kruskal–Wallis test. Pairwise comparisons were performed using Dunn's test with Bonferroni correction. Superscript letters indicate statistically significant differences between grades. *p<0.05 considered statistically significant; IQR: Interquartile range

Table 3. Correlation between Hoffa fat pad morphology, age, and meniscal grade

Variable	Spearman r	p
Hoffa thickness versus Meniscal grade	−0.254	0.002
Hoffa cross-sectional area versus Meniscal grade	−0.483	0.001
Age versus meniscal grade	0.191	0.022

Correlations were analyzed using Spearman's rank correlation coefficient. Spearman r indicates the strength and direction of the correlation: Positive r → direct relationship, Negative r → inverse relationship

Table 4. Univariable and multivariable ordinal logistic regression analyses of factors associated with higher MRI-based posterior horn meniscal grade

Variable	Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
Hoffa fat pad thickness (mm)	0.812 (0.710–0.930)	0.002	0.948 (0.800–1.123)	0.535
Hoffa cross-sectional area (mm ²)	0.989 (0.986–0.993)	<0.001*	0.985 (0.980–0.990)	<0.001*
Age (years)	1.035 (1.004–1.066)	0.025	1.016 (0.983–1.051)	0.345
Male sex (vs. female)	1.093 (0.609–1.965)	0.765	4.323 (1.921–9.728)	<0.001*
BMI (kg/m ²)	1.049 (0.957–1.150)	0.305	0.998 (0.901–1.105)	0.972

Lower Hoffa fat pad cross-sectional area and male sex were independently associated with higher MRI-based posterior horn meniscal grade after adjustment for age, sex, and BMI. OR: Odds ratio, CI: Confidence interval, BMI: Body mass index. Female was used as the reference category. *p<0.05 was considered statistically significant

Table 5. Hoffa fat pad thickness and cross-sectional area according to the pattern of posterior horn meniscal involvement

Parameter	Medial (n=132)	Medial+Lateral (n=12)	p
Hoffa thickness (mm)	20.83 (19–22)	20.92(18.5–23.25)	0.875
Hoffa cross-sectional area (mm ²)	552.89 (479–627)	500.33(461.25–537)	0.480

Data are presented as median (interquartile range). Differences between groups were assessed using the Mann–Whitney U test. P<0.05 was considered statistically significant. Owing to the small number of patients with combined medial and lateral involvement (n=12), this comparison should be interpreted with caution

with higher MRI-based posterior horn grades. Therefore, these findings should be interpreted with caution, and larger studies are needed to better define the effect of concomitant lateral meniscal involvement on Hoffa fat pad morphology.

DISCUSSION

Our study demonstrated a significant inverse association between Hoffa fat pad morphology and MRI-based posterior horn meniscal grade. Both sagittal thickness and

CSA decreased progressively with increasing MRI-based posterior horn meniscal grade. Among these measurements, CSA showed the strongest association with MRI grade and remained independently associated after adjustment for age, sex, and BMI.

The menisci are essential for load transmission and joint stability, and structural meniscal abnormalities are associated with knee osteoarthritis.^[1,2] MRI continues to be the gold standard in meniscal assessment, enabling accurate visualization of intrameniscal signal changes.^[3,12] However, a growing body of evidence indicates that knee degeneration is not cartilage and menisci alone, but rather extend also into neighboring soft tissue structures such as the IFP.^[4,5]

The IFP is now considered a metabolically active tissue that secretes proinflammatory cytokines and adipokines that may participate in the process of joint degeneration.^[5,6,13] Previous studies have mainly investigated the association between Hoffa fat pad morphology and osteoarthritis. For instance, Cai et al.^[7] reported an association between fat pad volume and structural knee changes, while Li et al.^[10] demonstrated that MRI-based radiomic features of the fat pad could predict osteoarthritis development. Similarly, Ruhdorfer et al.^[17] showed that differences in fat pad size and signal characteristics were associated with disease progression.

Contrary to these studies on osteoarthritis, the aim of our study was to investigate the association between Hoffa fat pad morphology and MRI-based posterior horn meniscal grade. Focusing on the posterior horn is clinically paramount because it bears the maximum mechanical stress during weight-bearing flexion, acting as the primary anchor against joint subluxation.^[1,2] The results of our study demonstrate that fat pad modifications strongly correlate with the degree of posterior horn meniscal grade. These morphological changes may be observed earlier in the degenerative cascade, prior to the appearance of late-stage osteoarthritis. Importantly, patients with chondromalacia and significant cartilage degeneration were excluded from the study. Therefore, the observed associations are less likely to be driven by concomitant cartilage pathology and may more specifically reflect the relationship between Hoffa fat pad morphology and meniscal grade. This design differs from previous studies investigating osteoarthritis or chondromalacia, in which cartilage abnormalities may have substantially influenced IFP morphology.

Interestingly, we observed a reduction in both thickness and CSA of the fat pad with increasing meniscal grade. While some studies have reported enlargement or increased signal intensity of the fat pad in inflammatory states,^[11,19] others have

suggested that chronic degeneration may lead to fibrosis, volume loss, or structural remodeling.^[17,18] Our findings support the latter hypothesis, indicating that progressive posterior horn meniscal grade may be associated with a reduction in fat pad size, possibly due to chronic mechanical stress or tissue remodeling processes driven by posterior joint compartment breakdown.

Unlike previous studies utilizing complex volumetric 3D segmentation or advanced radiomics analysis of the total IFP volume (e.g., Li et al.,^[10] Cai et al.,^[7]), our study utilized a single-slice sagittal CSA approach. While volumetric assessments provide a total representation of fat pad mass, they are computationally intensive, require dedicated commercial software, and are difficult to integrate into high-throughput clinical radiology workflows. Our findings suggest that a pragmatic, single-slice sagittal CSA measurement successfully captures the macro-structural remodeling of the IFP associated with intra-articular breakdown. Our findings suggest that a single-slice sagittal CSA measurement captures structural alterations of the Hoffa fat pad associated with MRI-based posterior horn meniscal abnormalities. The excellent intraobserver reproducibility observed in the present study supports the consistency of this measurement approach (ICC=0.929). Nevertheless, interobserver reproducibility was not evaluated, and further validation is required before routine clinical implementation can be recommended.

Of the parameters assessed, fat pad CSA was more strongly correlated with posterior horn meniscal grade than thickness. This result is in agreement with methodological studies demonstrating that CSA- or volume-based measures better represent global structural changes and are less affected by local anatomical variation.^[16,17] Crucially, our updated multivariate analysis revealed that male sex was also independently associated with higher posterior horn meniscal grades (OR=4.323, $p<0.001$). This structural divergence aligned with epidemiological data highlighting sex-specific variations in knee biomechanics, joint loading, and the baseline distribution of meniscal volume, suggesting that sex represents an essential covariate in structural joint remodeling. In the multivariable analysis, lower Hoffa fat pad CSA and male sex were independently associated with higher MRI-based posterior horn meniscal grade. Because sex distribution did not differ significantly among MRI grade groups in the univariable analysis, this finding should be interpreted with caution. It may reflect the effect of adjustment for other covariates rather than an isolated biological effect of sex. Further validation in independent cohorts is warranted.

In contrast, age and BMI were not independently associated with degeneration severity in the multivariate model. Previous

studies have suggested that these factors may influence Hoffa fat pad morphology and knee osteoarthritis development^[8,13] our findings indicate that Hoffa fat pad shape may be more indicative of local joint pathology rather than systemic influences when considering posterior horn meniscal grade. Although age demonstrated a weak positive correlation with meniscal grade in the univariate analysis, this association disappeared after adjustment for Hoffa fat pad morphology and other covariates. This finding suggests that local structural alterations within the knee joint may have a stronger relationship with grade severity than chronological age alone.

No significant differences in Hoffa fat pad morphology were observed between isolated medial and combined medial plus lateral posterior horn involvement. However, the combined involvement group was small and consisted exclusively of patients with higher MRI grades. Therefore, this comparison should be interpreted with caution, and further studies including larger numbers of patients with combined involvement are warranted.

Limitations

There are several limitations to be taken into account. First, the retrospective design of the study has potential for selection bias and does not allow for causal inference. Furthermore, because the study employed a grade-balanced sampling strategy, the regression-derived ORs represent adjusted associations within the selected cohort rather than population-level risk estimates or predictive performance. Second, the quantitative analysis was limited to single-slice sagittal parameters (thickness and CSA) rather than multislice or three-dimensional volumetric tracking. This strategy was intentionally chosen in view of the practical feasibility in routine clinical practice; however, it is still at a risk of slice-selection bias and underestimation of general volumetric discrepancy. Third, a single radiologist performed all image analyses; thus, interobserver variability was not assessed, constituting a methodological weakness for an operator-dependent manual tracing technique. Fourth, in patients who underwent bilateral knee MRI examinations, only one knee was included in the analysis, and the knee with the higher MRI-based posterior horn meniscal grade was selected. This approach may have introduced selection bias toward more advanced structural abnormalities. Fifth, our assessment focused entirely on the posterior horn segments of the menisci; consequently, potential structural cross-talk originating from isolated anterior horn or meniscal body pathologies was not thoroughly analyzed. Sixth, our cohort lacked specific patient-reported clinical metrics (such as visual analog scale or WOMAC scores) and radiographic osteoarthritis classifications (such as Kellgren-Lawrence grading). Although patients with severe osteoarthritis and significant cartilage degeneration

were excluded, early or subclinical osteoarthritic changes not detectable on routine MRI may still have influenced Hoffa fat pad morphology. Therefore, residual confounding related to underlying osteoarthritic changes cannot be completely excluded. Finally, without histopathological correlation, we cannot verify the tissue composition and inflammatory state of the Hoffa fat pad. Future prospective studies involving larger and more heterogeneous populations, naturally distributed MRI-based posterior horn meniscal grades, isolated lateral meniscal abnormalities, and interobserver validation are warranted to confirm and extend the present findings.

CONCLUSION

Our findings demonstrate that Hoffa fat pad morphology, particularly sagittal CSA, is inversely associated with MRI-based posterior horn meniscal grade. Among the evaluated imaging parameters, Hoffa fat pad CSA remained independently associated with higher MRI-based posterior horn meniscal grade after adjustment for demographic variables. These findings suggest that Hoffa fat pad CSA may serve as a useful MRI-derived morphological marker associated with structural meniscal abnormalities. However, because of the retrospective cross-sectional design, intentional grade-balanced sampling strategy, and absence of interobserver validation, the observed associations should not be interpreted as evidence of causality, predictive performance, or population-level risk. Prospective longitudinal studies are needed to confirm these findings and determine their clinical applicability.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Gaziantep University Ethics Committee (No: 2026/139, Date: 18/02/2026).

Informed Consent: Due to the retrospective study design, the requirement for informed consent was waived.

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Association Between Admission Inflammatory Indices and Surgically Confirmed Hollow Viscus Injury in Abdominal and Thoracoabdominal Stab Wounds: A Retrospective Observational Study

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ABSTRACT

Objective: This study evaluated the association between admission inflammatory indices and surgically confirmed hollow viscus injury in patients undergoing surgery for abdominal or thoracoabdominal stab wounds.

Materials and Methods: Patients aged 16 years or older who underwent surgery between January 2015 and December 2023 were retrospectively reviewed. Patients with diaphragmatic, concomitant intra-abdominal solid-organ or vascular or extra-abdominal injuries, those requiring another surgical specialty, and those undergoing tube thoracostomy were excluded. Fifty patients with hollow viscus injury and 50 without hollow viscus injury were included. Admission laboratory parameters and derived inflammatory indices were assessed using logistic regression and receiver operating characteristic analysis.

Results: The mean age of the 100 patients was 31.4±11.6 years, and 95% were male. Neutrophil, monocyte, platelet, C-reactive protein (CRP), and several derived inflammatory indices were higher in patients with hollow viscus injury, whereas the lymphocyte-to-monocyte ratio (LMR) and lymphocyte-to-CRP ratio were lower. Platelet count (odds ratio [OR]=1.008; 95% confidence interval [CI], 1.001–1.015; p=0.036) and LMR (OR=0.679; 95% CI, 0.559–0.825; p<0.001) were independently associated with hollow viscus injury. The area under the curve for LMR was 0.764 (95% CI, 0.671–0.857). An LMR cutoff of <5.5 yielded 64% sensitivity and 80% specificity.

Conclusion: A lower admission LMR and a higher platelet count were independently associated with surgically confirmed hollow viscus injury. LMR is insufficient as a stand-alone diagnostic test but may provide a low-cost adjunct to clinical and radiological assessment. Validation in larger independent cohorts is required.

Keywords: Abdominal stab wound, Hollow viscus injury, Inflammatory indices, Lymphocyte-to-monocyte ratio, Platelet count, Thoracoabdominal stab wound

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INTRODUCTION

Abdominal and thoracoabdominal stab wounds are among the most challenging clinical presentations in trauma surgery because a seemingly limited external wound may cause injuries of varying depth involving the peritoneum, diaphragm, or gastrointestinal tract.^[1,2] The primary clinical challenge in these patients is not merely to establish peritoneal violation but to identify, at an early stage and with adequate reliability, a hollow viscus injury requiring urgent surgical treatment.^[2,3] The indication for surgery is generally clear in the presence of hemodynamic instability, generalized peritonitis, or evisceration. In contrast, clinical decision-making becomes more challenging in hemodynamically stable patients with limited physical examination findings and equivocal radiological findings.^[3,4]

A missed hollow viscus injury may result in leakage of intestinal contents into the peritoneal cavity, delayed peritonitis, sepsis, and increased morbidity and mortality. Conversely, unnecessary surgical exploration in patients without an intra-abdominal injury requiring operative treatment may lead to avoidable adverse outcomes, including anesthesia-related complications, surgical site infection, adhesions, incisional hernia, and prolonged hospitalization.^[3-5] Balancing these opposing risks forms the basis of selective management strategies for abdominal and thoracoabdominal stab wounds.^[3] Current practice supports the combined use of serial physical examinations, laboratory investigations, and contrast-enhanced computed tomography rather than routine laparotomy in hemodynamically stable patients without signs of peritonitis.^[3,6] Although diagnostic laparoscopy is effective for detecting peritoneal violation and diaphragmatic injury, it has limitations, including its invasive nature and the potential for small perforations to be missed when the gastrointestinal tract cannot be examined completely.^[4,5]

Contrast-enhanced computed tomography is a key imaging modality for evaluating organ injuries and wound trajectories in hemodynamically stable patients with penetrating trauma.^[6,7] Although direct findings such as free intraperitoneal air, bowel wall discontinuity, and extravasation of enteric contrast material have high specificity, they are not present in every patient. Indirect findings, including free fluid, bowel wall thickening, and mesenteric infiltration, may occur in different types of injury.^[6,7] A recent study evaluating patients with penetrating abdominal trauma reported that computed tomography had high sensitivity and a high negative predictive value but low specificity for detecting hollow viscus injury.^[7] These limitations highlight the need for rapid, readily available, and reproducible biomarkers that could support clinical assessment, particularly when clinical and radiological findings are discordant.

Traumatic tissue injury induces an early and dynamic systemic inflammatory response involving both the innate and adaptive immune systems.^[8,9] During this process, changes may occur in the total leukocyte count as well as in the numbers, distribution, and functions of neutrophils, lymphocytes, and monocytes. Although neutrophilia and lymphopenia are frequently observed during the early period after trauma, the magnitude and temporal course of these changes may vary according to injury severity and the patient's clinical condition.^[8-10] Platelet count may be influenced by bleeding, consumptive coagulopathy, resuscitation, and the inflammatory response. C-reactive protein (CRP) levels may remain normal or only slightly elevated immediately after trauma but may increase substantially over the subsequent days.^[11] These hematological and inflammatory changes have provided the basis for investigating markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), lymphocyte-to-CRP ratio (LCR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) in trauma patients.^[12,13] However, previous studies have primarily focused on prognostic outcomes such as acute kidney injury, mortality, and in-hospital outcomes, whereas evidence regarding surgically confirmed isolated hollow viscus injury remains limited.^[12,13]

This study aimed to evaluate the associations of routine hematological and biochemical parameters obtained at admission, together with the inflammatory indices derived from these parameters, with surgically confirmed hollow viscus injury in patients undergoing surgical exploration for abdominal or thoracoabdominal stab wounds. We also aimed to identify parameters independently associated with hollow viscus injury and to evaluate the discriminative performance and potential cutoff value of the inflammatory index that remained independently significant in the multivariable analysis.

MATERIALS AND METHODS

Study Design and Patient Selection

This single-center, retrospective, observational study reviewed the electronic medical records and operative reports of patients aged 16 years or older who underwent surgery for abdominal or thoracoabdominal stab wounds between January 2015 and December 2023. Of the 453 patients who underwent surgery during the study period, hollow viscus injury was identified during surgical exploration in 154 patients, whereas no hollow viscus injury was found in 299 patients.

Patients with diaphragmatic injury, concomitant intra-abdominal solid organ or vascular injury, an injury requiring intervention

by another surgical specialty, or a concomitant extra-abdominal injury, as well as those who underwent tube thoracostomy, were excluded. After the exclusion criteria were applied, 50 eligible patients comprised the hollow viscus injury-positive (HVIP) group, and 50 comprised the hollow viscus injury-negative (HVIN) group. All patients who met the eligibility criteria were included in the analysis, resulting in a final study population of 100 patients. The patient selection process is presented in Figure 1.

A full-thickness injury to the wall of the stomach, small intestine, colon, or rectum identified during surgery was defined as a hollow viscus injury. The primary outcome was hollow viscus injury confirmed by surgical exploration. Operative findings were used as the reference standard for classifying patients into the HVIP and HVIN groups.

The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (decision date: January 22, 2024; decision no.: 2024-01-31). The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant national regulations.

Data Collection

The recorded patient characteristics included age, sex, body mass index, comorbidities, smoking and alcohol use, history of abdominal surgery, American Society of Anesthesiologists (ASA) physical status classification, and Charlson Comorbidity Index (CCI). Injury location, presence of peritonitis at admission, time from hospital admission to surgery, surgical approach, duration of surgery, injured organs, surgical procedures performed, post-operative complications, length of hospital stay, and in-hospital mortality were also evaluated.

Laboratory analyses were based on the first venous blood samples obtained upon admission to the emergency department within the first 6 h after injury. All blood samples included in the analysis were collected before surgical intervention. White blood cell, neutrophil, lymphocyte, monocyte, and platelet counts and CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate levels were recorded. Blood cell counts were expressed as $\times 10^3/\mu\text{L}$, CRP as mg/dL, AST and ALT as U/L, and lactate as mmol/L. To avoid a mathematically undefined result when calculating LCR, CRP values reported as zero were assigned a value of 0.1 mg/dL solely for this calculation.

Inflammatory Indices

The NLR, PLR, LMR, LCR, SII, SIRI, and AISI were calculated using the laboratory values obtained at admission.

The following formulas were used: $\text{NLR} = \text{Neutrophil count} / \text{Lymphocyte count}$; $\text{PLR} = \text{Platelet count} / \text{Lymphocyte count}$;

$\text{LMR} = \text{Lymphocyte count} / \text{Monocyte count}$; $\text{LCR} = \text{Lymphocyte count} / \text{CRP}$; $\text{SII} = (\text{Platelet count} \times \text{Neutrophil count}) / \text{Lymphocyte count}$; $\text{SIRI} = (\text{Neutrophil count} \times \text{Monocyte count}) / \text{Lymphocyte count}$; and $\text{AISII} = (\text{Neutrophil count} \times \text{Monocyte count} \times \text{Platelet count}) / \text{Lymphocyte count}$.

Computed Tomography Assessment

Pre-operative computed tomography findings were classified according to the presence or absence of predefined findings considered suspicious for perforation, based on the official radiology reports. Bowel wall discontinuity, findings explicitly interpreted as direct evidence of perforation in the radiology report, or free intraperitoneal air was considered suspicious for perforation. Because free intraperitoneal air may enter the peritoneal cavity through the penetrating wound tract, this finding alone was not considered definitive evidence of perforation. The computed tomography classification was compared with the findings of surgical exploration.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 26.0. The normality of continuous variables was evaluated using the Shapiro–Wilk test and graphical methods. Normally distributed continuous variables are presented as mean $\pm$ standard deviation, non-normally distributed continuous variables as median and interquartile range, and categorical variables as number and percentage.

Continuous variables were compared between the HVIP and HVIN groups using the independent-samples t-test or Mann–Whitney U test, as appropriate for their distributions. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test, as appropriate. Missing values were not imputed, and analyses for each variable were performed using the available data.

Variables associated with hollow viscus injury were initially evaluated using univariable logistic regression analysis. Variables that were statistically significant in the univariable analysis and available before surgery were entered into a multivariable logistic regression model using the forward stepwise likelihood-ratio method. Variables determined during or after surgical exploration, such as duration of surgery, surgical approach, and length of hospital stay, were not included in the diagnostic multivariable model. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). The OR for platelet count was calculated for each $1 \times 10^3/\mu\text{L}$ increase.

The ability of the inflammatory index that remained independently associated with hollow viscus injury in the multivariable analysis to discriminate between the HVIP

and HVIN groups was evaluated using receiver operating characteristic (ROC) analysis. The area under the ROC curve and its 95% CI were calculated. The optimal cutoff value was determined using the Youden index, which maximizes the sum of sensitivity and specificity. Sensitivity, specificity, and sample-specific positive and negative predictive values were calculated for the identified cutoff. Statistical significance was set at $p < 0.05$.

RESULTS

Patient Selection and Overall Characteristics

A total of 453 patients who underwent surgery for abdominal or thoracoabdominal stab wounds during the study period were evaluated. Hollow viscus injury was identified during surgical exploration in 154 patients, whereas no hollow viscus injury was found in 299 patients. After the exclusion criteria were applied, 104 patients with hollow viscus injury and 249 patients without hollow viscus injury were excluded. The remaining 50 eligible

patients comprised the HVIP group, and 50 comprised the HVIN group. All eligible patients were included in the analysis, resulting in a final study population of 100 patients (Fig. 1).

Patient ages ranged from 16 to 76 years. The mean age was 31.4 ± 11.6 years, and the median age was 29.5 years. The study population included 95 men (95%) and five women (5%). The mean body mass index was 24.9 ± 3.8 kg/m². Six patients (6%) were classified as ASA I, 66 (66%) as ASA II, 24 (24%) as ASA III, and four (4%) as ASA IV. The CCI was zero in 93 patients (93%). Smoking was reported in 49 patients (49%), alcohol use in 26 (26%), comorbidities in nine (9%), and a history of abdominal surgery in 12 (12%). Signs of peritonitis were present at emergency department admission in five patients (5%).

Comparison of Demographic and Clinical Characteristics

The median age was 29.5 (19.8–38.5) years in the HVIN group and 29.5 (23.0–38.0) years in the HVIP group, with no significant

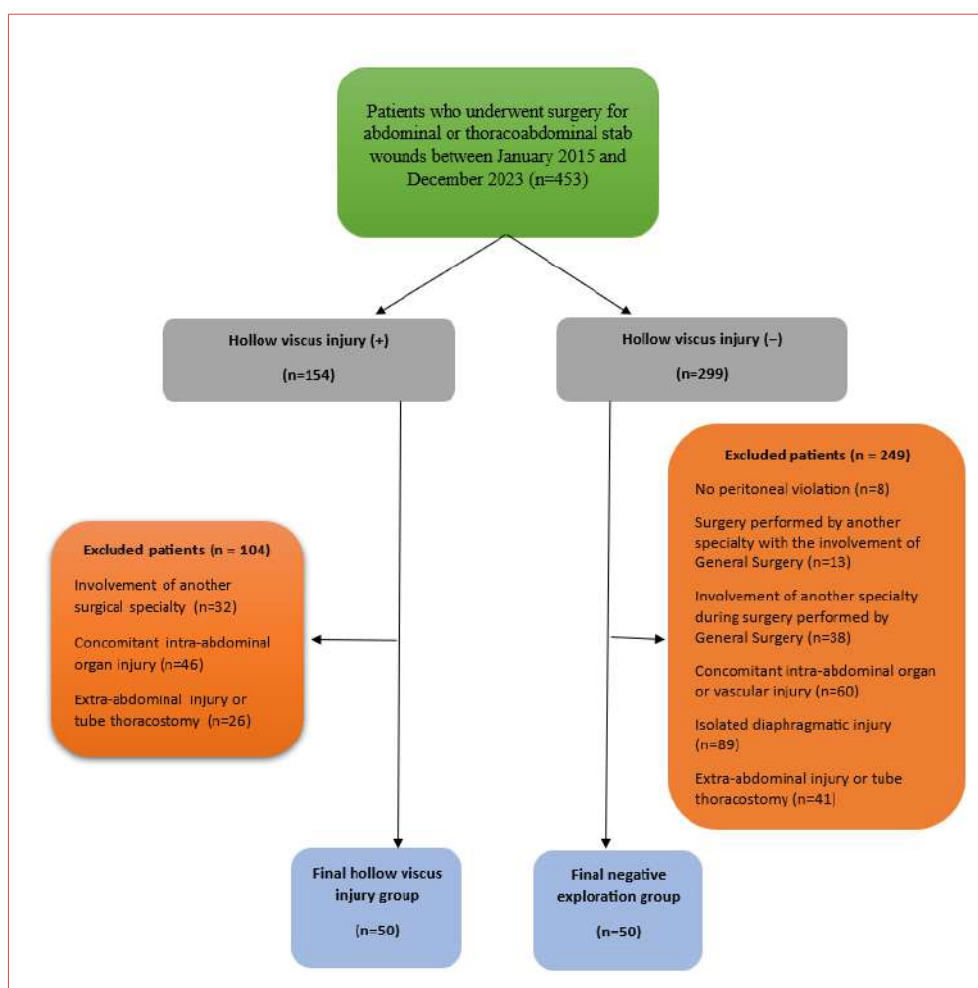


Figure 1. Flowchart of patient selection and allocation to the hollow viscus injury and negative exploration groups.

between-group difference ($p=0.486$). Men accounted for 96% of the HVIN group and 94% of the HVIP group ($p=0.646$). The mean body mass index was 24.5 ± 3.0 kg/m² in the HVIN group and 25.3 ± 4.4 kg/m² in the HVIP group ($p=0.294$).

The distribution of ASA physical status classifications differed significantly between the groups ($p=0.001$). In the HVIN group, 80% of patients were classified as ASA II, whereas the proportions of ASA II and ASA III patients in the HVIP group were 52% and 40%, respectively. The difference in the distribution of the CCI did not reach statistical significance ($p=0.050$). No significant between-group differences were observed in smoking ($p=0.072$), alcohol use ($p=0.362$), presence of comorbidities ($p=0.081$), history of abdominal surgery ($p=0.538$), or signs of peritonitis at admission ($p=0.169$).

Injury-location data were unavailable for four patients. In the available-case analysis, abdominal injury locations were recorded more frequently in the HVIP group, whereas thoracoabdominal injury locations were recorded more frequently in the HVIN group ($p<0.001$ for both). Demographic and clinical characteristics according to study group are presented in Table 1.

Laboratory Findings

The median CRP level was significantly higher in the HVIP group than in the HVIN group (2.0 [1.0–5.0] vs. 1.0 [0.1–3.0] mg/dL; $p=0.006$). The median white blood cell count was 11.0 (7.0 – 13.0) $\times 10^3/\mu\text{L}$ in the HVIN group and 12.0 (10.0 – 15.0) $\times 10^3/\mu\text{L}$ in the HVIP group. Despite the higher value in the HVIP group, the difference did not reach statistical significance ($p=0.057$).

The median neutrophil count was significantly higher in the HVIP group than in the HVIN group (7.75 [5.88–14.13] vs. 5.60 [4.20–7.83] $\times 10^3/\mu\text{L}$; $p<0.001$). The median monocyte count was also higher in the HVIP group (0.65 [0.50–0.93] vs. 0.50 [0.40–0.70] $\times 10^3/\mu\text{L}$; $p=0.001$).

The median lymphocyte count was 3.50 (2.48 – 5.35) $\times 10^3/\mu\text{L}$ in the HVIN group and 3.00 (2.00 – 4.05) $\times 10^3/\mu\text{L}$ in the HVIP group. Although the value was lower in the HVIP group, the difference did not reach statistical significance ($p=0.064$). The median platelet count was significantly higher in the HVIP group than in the HVIN group (289 [243.8–325.3] vs. 244 [214.5–291.5] $\times 10^3/\mu\text{L}$; $p=0.007$). No significant differences were observed in AST ($p=0.871$), ALT ($p=0.632$), lactate ($p=0.954$), or the AST/ALT ratio ($p=0.677$).

Comparison of Inflammatory Indices

The median LMR was significantly lower in the HVIP group than in the HVIN group (4.37 [2.59–6.85] vs. 7.29 [5.76–8.81];

$p<0.001$). In contrast, NLR, PLR, SII, SIRI, and AISI were all significantly higher in the HVIP group.

The median NLR values in the HVIN and HVIP groups were 1.52 (1.14–2.01) and 2.60 (1.40–6.42), respectively ($p=0.001$), and the corresponding PLR values were 74.83 (50.77–88.72) and 95.21 (60.44–163.16) ($p=0.005$). Median SII values were 393.49 (253.96–522.88) in the HVIN group and 875.38 (399.76–1954.82) in the HVIP group ($p<0.001$). The median SIRI was 0.72 (0.53–1.21) in the HVIN group and 1.82 (0.81–5.51) in the HVIP group ($p<0.001$), whereas the corresponding AISI values were 188.59 (127.61–309.23) and 563.88 (227.08–1582.91) ($p<0.001$).

The median LCR was significantly lower in the HVIP group than in the HVIN group (1.60 [0.42–3.41] vs. 3.57 [1.23–18.00]; $p=0.005$). Comparisons of laboratory findings and inflammatory indices between the study groups are presented in Table 2.

Computed Tomography Findings

All 100 patients underwent pre-operative computed tomography. None of the patients in the HVIN group had a predefined finding considered suspicious for perforation. In the HVIP group, the radiology reports described direct findings suggestive of perforation in 12 patients and free intraperitoneal air in three. Because free intraperitoneal air was considered suspicious for perforation, these three patients were also classified as radiologically positive.

Consequently, 15 patients (30%) in the HVIP group had computed tomography findings suspicious for perforation, whereas none of the predefined suspicious findings were identified in the remaining 35 patients (70%). Computed tomography findings suspicious for perforation were significantly more frequent in the HVIP group ($p<0.001$).

Operative Findings and Surgical Outcomes

The median time from hospital admission to surgery was 15 (4.5–31.0) h in the HVIN group and 4 (2.5–7.0) h in the HVIP group. Patients in the HVIP group underwent surgery significantly earlier ($p<0.001$). The median duration of surgery was significantly longer in the HVIP group than in the HVIN group (115 [90.0–150.0] vs. 29 [20.0–61.3] min; $p<0.001$).

In the HVIN group, 43 of 50 patients (86%) underwent laparoscopic exploration and seven (14%) underwent laparotomy. In the HVIP group, six of 50 patients (12%) underwent laparoscopic exploration and 44 (88%) underwent laparotomy. The proportion of patients undergoing laparotomy was significantly higher in the HVIP group ($p<0.001$).

Among the 50 patients in the HVIP group, gastric injury was identified in 20 (40%), small bowel injury in 26 (52%), colonic

Table 1. Comparison of demographic, clinical, radiological, operative, and post-operative characteristics between the study groups

	HVIN (n=50)		HVIP (n=50)		p
	Mean±SD/n (%)	Median	Mean±SD/n (%)	Median	
Age (years)	30.3±10.8	29.5	32.4±12.2	29.5	0.486 ^m
Sex					
Male	48 (96.0)		47 (94.0)		0.646 ^{χ²}
Female	2 (4.0)		3 (6.0)		
BMI	24.5±3.0	24.4	25.3±4.4	24.8	0.294 ^t
ASA physical status					
I	5 (10.0)		1 (2.0)		0.001 ^{χ²}
II	40 (80.0)		26 (52.0)		
III	4 (8.0)		20 (40.0)		
IV	1 (2.0)		3 (6.0)		
CCI					
0	49 (98.0)		44 (88.0)		0.050 ^{χ²}
1	1 (2.0)		3 (6.0)		
2	0 (0.0)		1 (2.0)		
3	0 (0.0)		1 (2.0)		
4	0 (0.0)		1 (2.0)		
Smoking	20 (40.0)		29 (58.0)		0.072 ^{χ²}
Alcohol use	11 (22.0)		15 (30.0)		0.362 ^{χ²}
Comorbidity	2 (4.0)		7 (14.0)		0.081 ^{χ²}
Previous abdominal surgery	5 (10.0)		7 (14.0)		0.538 ^{χ²}
Injury location					
Abdominal	12 (25.0)		29 (60.4)		<0.001 ^{χ²}
Thoracoabdominal	40 (83.3)		19 (39.6)		<0.001 ^{χ²}
Other	1 (2.1)		4 (8.3)		0.168 ^{χ²}
CT finding suspicious for perforation	0 (0.0)		15 (30.0)		<0.001 ^{χ²}
Time from hospital admission to surgery (hours)	22.8±25.8	15.0	5.4±3.8	4.0	<0.001 ^m
Duration of surgery (min)	44.9±41.4	29.0	121.7±42.5	115.0	<0.001 ^m
Surgical approach					
Laparoscopic	43 (86.0)		6 (12.0)		<0.001 ^{χ²}
Open	7 (14.0)		44 (88.0)		
Post-operative complication	0 (0.0)		1 (2.0)		1.000 ^{χ²}
Length of hospital stay (days)	2.2±1.5	2.0	5.4±2.0	5.0	<0.001 ^m

ASA: American Society of Anesthesiologists, BMI: Body mass index, CCI: Charlson comorbidity index, CT: Computed tomography, HVIN: Hollow viscus injury negative, HVIP: Hollow viscus injury positive, SD: Standard deviation. Statistical tests: t, independent-samples t-test, m: Mann–Whitney U test, χ^2 : Chi-square test

injury in 12 (24%), and rectal injury in two (4%). Because some patients had injuries involving more than one hollow viscus, the sum of organ-specific counts exceeded the number of patients.

The surgical procedures included gastric repair in 20 patients (40%), small bowel repair in 20 (40%), colonic repair in eight (16%), and rectal repair in two (4%). Small bowel resection was

Table 2. Comparison of admission laboratory parameters and systemic inflammatory indices between the study groups

	HVIN (n=50)		HVIP (n=50)		p
	Mean±SD/n-%	Median	Mean±SD/n-%	Median	
CRP (mg/dL)	2.9±5.9	1.0	5.6±13.5	2.0	0.006 ^m
WBC count (×10 ³ /μL)	10.8±3.9	11.0	12.9±5.3	12.0	0.057 ^m
Neutrophil count (×10 ³ /μL)	6.4±3.3	5.6	11.0±9.4	7.8	<0.001 ^m
Lymphocyte count (×10 ³ /μL)	3.9±1.7	3.5	3.3±1.8	3.0	0.064 ^m
Monocyte count (×10 ³ /μL)	0.57±0.24	0.50	0.96±1.06	0.65	0.001 ^m
Platelet count (×10 ³ /μL)	257.6±65.1	244.0	288.5±61.1	289.0	0.007 ^m
AST (U/L)	26.9±15.9	22.0	25.9±15.5	23.0	0.871 ^m
ALT (U/L)	24.6±17.2	19.0	23.1±16.6	18.5	0.632 ^m
Lactate (mmol/L)	4.4±3.1	3.7	4.4±3.2	3.6	0.954 ^m
LMR	7.6±3.8	7.3	4.6±2.5	4.4	<0.001 ^m
NLR	2.1±2.4	1.5	5.1±5.7	2.6	0.001 ^m
PLR	76.5±33.4	74.8	125.1±93.6	95.2	0.005 ^m
LCR	10.8±15.8	3.6	4.5±11.3	1.6	0.005 ^m
SII	524.0±594.0	393.5	1498.0±1768.0	875.4	<0.001 ^m
SIRI	1.5±2.8	0.7	6.1±13.6	1.8	<0.001 ^m
AISI	367.1±675.8	188.6	1880.8±4149.1	563.9	<0.001 ^m
AST/ALT ratio	1.26±0.50	1.17	1.34±0.72	1.23	0.677 ^m

AISI: Aggregate index of systemic inflammation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, HVIN: Hollow viscus injury negative, HVIP: Hollow viscus injury positive, LCR: Lymphocyte-to-C-reactive protein ratio, LMR: Lymphocyte-to-monocyte ratio, m: Mann-Whitney U test, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index. WBC: White blood cell

performed in six patients (12%), and colonic resection in four (8%). Because more than one repair or resection procedure could be performed in the same patient, the sum of the procedure-specific percentages exceeded 100%.

Post-operative Outcomes

A subcutaneous abscess developed in one patient (2%) in the HVIP group, whereas no post-operative complications occurred in the HVIN group. The complication rates did not differ significantly between the groups ($p=1.000$). No in-hospital deaths occurred in either group.

The median length of hospital stay was 2 (1–3) days in the HVIN group and 5 (4–6) days in the HVIP group. Hospital stay was significantly longer in the HVIP group ($p<0.001$). Between-group comparisons of computed tomography findings, surgical characteristics, and post-operative outcomes are also presented in Table 1.

Logistic Regression Analysis

In the univariable logistic regression analysis, ASA physical status, injury location, neutrophil, monocyte, and platelet

counts, and LMR, NLR, PLR, LCR, SII, SIRI, and AISI were significantly associated with hollow viscus injury. The results of the univariable and multivariable logistic regression analyses are presented in Table 3.

In the multivariable logistic regression analysis performed using the forward likelihood-ratio method, platelet count and LMR remained independently associated with hollow viscus injury. Each $1 \times 10^3/\mu\text{L}$ increase in platelet count was positively associated with hollow viscus injury ($\text{OR}=1.008$; 95% CI, 1.001–1.015; $p=0.036$). Each one-unit increase in LMR was inversely associated with hollow viscus injury ($\text{OR}=0.679$; 95% CI, 0.559–0.825; $p<0.001$).

In the logistic regression model in which LMR was the sole predictor, the predicted probability of hollow viscus injury decreased as LMR increased (Fig. 2).

ROC Analysis

In the ROC analysis evaluating the ability of LMR to discriminate between the HVIP and HVIN groups, the area under the curve

Table 3. Univariable and multivariable logistic regression analyses for hollow viscus injury

	Univariable model					Multivariable model				
	OR	95% CI			p	OR	95% CI			p
CRP	1.034	0.976	-	1.095	0.260					
Neutrophil count	1.190	1.064	-	1.331	0.002					
Monocyte count	9.919	1.833	-	53.68	0.008					
Platelet count	1.008	1.001	-	1.015	0.019	1.008	1.001	-	1.015	0.036
LMR	0.686	0.571	-	0.826	<0.001	0.679	0.559	-	0.825	<0.001
NLR	1.269	1.073	-	1.501	0.005					
PLR	1.014	1.005	-	1.024	0.004					
LCR	0.960	0.923	-	0.999	0.043					
SII	1.001	1.000	-	1.002	0.002					
SIRI	1.239	1.048	-	1.466	0.012					
AISI	1.001	1.000	-	1.002	0.007					

The multivariable logistic regression model was constructed using the forward likelihood-ratio method. AISI: Aggregate index of systemic inflammation, CI: Confidence interval, CRP: C-reactive protein, LCR: Lymphocyte-to-C-reactive protein ratio, LMR: Lymphocyte-to-monocyte ratio, LR: Likelihood ratio, NLR: Neutrophil-to-lymphocyte ratio, OR: Odds ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index

was 0.764 (95% CI, 0.671–0.857; $p<0.001$ (Table 4 and Fig. 3). The optimal LMR cutoff determined using the Youden index was 5.5. When an LMR of <5.5 was considered positive, sensitivity was 64.0%, specificity was 80.0%, the positive predictive value was 76.2%, and the negative predictive value was 69.0%.

Among the 42 patients with an LMR of <5.5 , 32 were in the HVIP group, and 10 were in the HVIN group. Of the 58 patients with an LMR of ≥ 5.5 , 18 were in the HVIP group, and 40 were in the HVIN group. The positive and negative predictive values were considered specific to the present study sample, which included equal numbers of patients in the HVIP and HVIN groups.

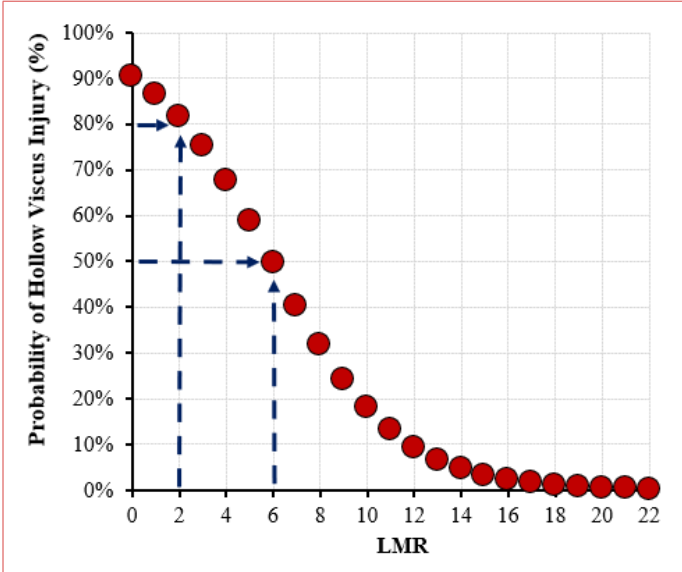


Figure 2. Predicted probability of hollow viscus injury according to LMR.

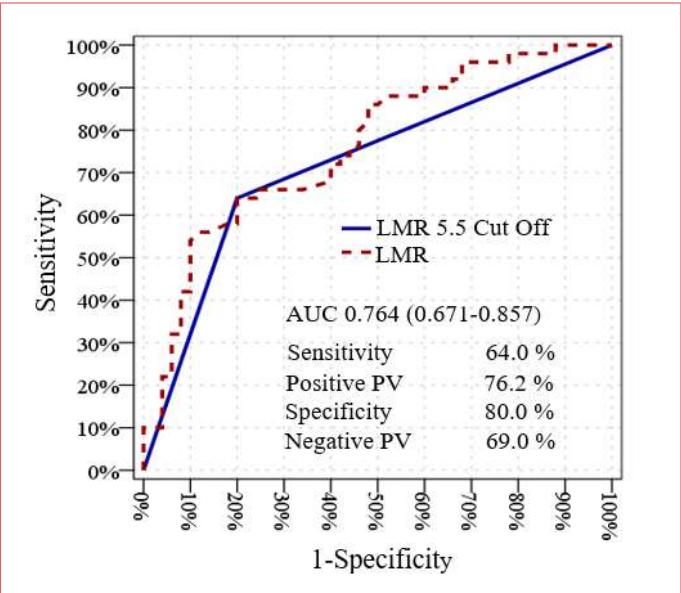


Figure 3. Receiver operating characteristic curve of LMR for predicting hollow viscus injury.

Table 4. ROC analysis and diagnostic performance of LMR

	AUC		95% CI		p
LMR	0.764		0.671	0.857	<0.001
LMR <5.5 Cut Off	0.720		0.618	0.822	<0.001
	HVIN (n=50)	HVIP (n=50)			%
LMR category					
<5.5	10	32	Sensitivity		64.0
≥5.5	40	18	Positive predictive value		76.2
			Specificity		80.0
			Negative predictive value		69.0

The optimal cutoff value was determined using the Youden index. AUC: Area under the curve, CI: Confidence interval, HVIN: Hollow viscus injury negative, HVIP: Hollow viscus injury positive, LMR: Lymphocyte-to-monocyte ratio, ROC: Receiver operating characteristic

DISCUSSION

This study investigated the association between inflammatory markers obtained at admission and surgically confirmed hollow viscus injury in a selected cohort of patients who underwent surgery for abdominal or thoracoabdominal stab wounds. Neutrophil, monocyte, platelet, CRP, NLR, PLR, SII, SIRI, and AISI values were higher in the HVIP group, whereas LMR and LCR were lower. Only platelet count and LMR retained independent associations with hollow viscus injury in the multivariable analysis. The area under the ROC curve for LMR was 0.764, and a cutoff value of 5.5 yielded a sensitivity of 64% and a specificity of 80%. These findings suggest that LMR is insufficient to establish or exclude hollow viscus injury when used alone but may serve as an adjunct to clinical and radiological assessment.

Traumatic tissue injury induces an early inflammatory and immune response involving neutrophils, monocytes, lymphocytes, and platelets. Ratios incorporating different cell populations may therefore reflect the systemic response to trauma more comprehensively than a single cell count. In our study, differences in total white blood cell and lymphocyte counts did not reach statistical significance, whereas neutrophil and monocyte counts and the indices derived from these cells differed significantly between the groups. These findings are consistent with the biological basis of the cellular response to trauma described in previous studies.^[8,9]

Yucel et al.^[14] evaluated patients with penetrating abdominal stab wounds and reported higher white blood cell, neutrophil, monocyte, NLR, and PLR values and lower lymphocyte counts among patients who subsequently required surgery. They also showed that NLR and PLR could contribute to identifying the need for surgery. However, their study compared surgically treated patients with those managed non-operatively, whereas

all patients in our study underwent surgical exploration and were classified according to the presence or absence of hollow viscus injury confirmed at surgery.

Demirpolat and Islam reported that NLR, PLR, and SII values measured at admission did not discriminate the need for surgery, whereas values measured during follow-up could predict therapeutic surgery.^[15] In contrast, admission NLR, PLR, and SII values differed significantly between the HVIP and HVIN groups in our study. This difference between studies may be attributable to differences in patient selection, the timing of blood sampling, and the outcomes evaluated. The exclusion of concomitant organ and vascular injuries in our study may also have reduced their confounding effects on the inflammatory response.

In a recent study, Colapkulu-Akgul et al.^[16] evaluated initial complete blood count parameters and computed tomography findings in 91 patients who underwent laparotomy for abdominal stab wounds. The investigators reported that NLR, PLR, free air, and free fluid did not reliably predict therapeutic laparotomy. This finding is consistent with our observation that NLR and PLR differed between the study groups but lost their independent associations in the multivariable analysis. In contrast, the independent association of LMR suggests that inflammatory indices incorporating the monocyte component warrant further investigation in this patient population.

One of the most notable findings of our study was the independent association between a lower LMR and hollow viscus injury. Combining an increase in monocyte count with a relative decrease in lymphocyte count within a single ratio may have revealed a distinction that was not evident from either cell count alone. A higher monocyte-to-lymphocyte ratio has previously been associated with adverse clinical outcomes in patients with abdominal trauma. Because the

monocyte-to-lymphocyte ratio is the mathematical inverse of LMR, the direction of this association is consistent with the lower LMR observed in our study. However, previous studies have primarily evaluated prognostic outcomes such as mortality and organ failure rather than the detection of hollow viscus injury.^[13]

Platelet count was also independently associated with hollow viscus injury in the multivariable analysis. The platelet response after trauma follows a time-dependent course. During the early period, platelet counts may decrease because of hemorrhage, consumption, dilution, shock, and resuscitation, whereas bone marrow activity and inflammatory stimulation may subsequently lead to platelet recovery and reactive thrombocytosis. In a prospective study of 276 patients with major trauma, Schofield et al.^[17] reported that immature platelets exhibited distinct early and late dynamics and that these changes were associated with clinical outcomes. Similarly, Rossetto et al.^[18] in a cohort of 803 critically ill trauma patients, demonstrated that platelet counts initially decreased after injury, generally reached their nadir within 48–72 h, recovered by approximately day 7, and could rise above the normal range by day 14. However, all blood samples in our study were obtained within the first 6 h after injury, and the median platelet counts in both the HVIN and HVIP groups remained within normal laboratory reference ranges (244 and $289 \times 10^3/\mu\text{L}$, respectively). Therefore, the higher platelet count observed in the HVIP group represents an early relative difference in platelet count rather than thrombocytosis or a delayed bone marrow response. Because platelet function was not evaluated and the biological mechanism underlying this association cannot be determined from the observational study design, this finding should be interpreted as an adjunctive marker rather than a mechanistic observation or a stand-alone diagnostic indicator.

Although NLR, PLR, SII, SIRI, and AISI were higher in the HVIP group, they did not retain independent associations in the multivariable analysis. Because these indices are derived from the same neutrophil, lymphocyte, monocyte, and platelet measurements, they may be strongly correlated mathematically. Furthermore, the limited sample size may have made it difficult to distinguish the independent contributions of several interrelated indices. The significant between-group differences in these indices should therefore not be disregarded, but the indices should not be interpreted as independent diagnostic markers.

Predefined computed tomography findings considered suspicious for perforation were identified in only 30% of patients in the HVIP group. The absence of these findings in 70% of patients with HVIP indicates that the absence of direct

signs of perforation cannot, by itself, exclude hollow viscus injury in this selected operative population. However, only findings explicitly reported as direct evidence of perforation and free intraperitoneal air were classified as positive in our study. Therefore, this proportion should not be interpreted as the overall sensitivity of computed tomography for all bowel and mesenteric injury findings. The WSES guidelines similarly recommend that imaging findings be interpreted together with clinical assessment and serial physical examinations.^[19]

Although free intraperitoneal air was considered suspicious for perforation, it may have entered the peritoneal cavity through the penetrating wound tract. Kong et al.^[20] evaluated patients with isolated pneumoperitoneum following abdominal stab wounds and reported that approximately one-third had no intra-abdominal injury. Free intraperitoneal air should therefore be regarded as a finding that increases the likelihood of perforation but does not provide a definitive diagnosis when considered alone.

The main limitations of this study were its retrospective, single-center design, limited sample size, and inclusion of only surgically treated patients. Because patients managed non-operatively were not evaluated, the performance of LMR for determining the need for surgery could not be investigated. Although excluding concomitant injuries reduced potential confounding, it also limited the generalizability of the findings to patients with multiple trauma. The interval between injury and blood sampling was not standardized, and inflammatory markers were measured only at admission, preventing assessment of their temporal changes. The computed tomography classification was based on official radiology reports rather than a standardized retrospective review of the images; therefore, differences in imaging protocols and reporting radiologists could not be controlled. In addition, evaluating several mathematically correlated inflammatory indices in a limited sample may have increased the risk of model instability and chance findings. Because the HVIP and HVIN groups contained equal numbers of patients and did not reflect the true clinical prevalence of hollow viscus injury, the positive and negative predictive values are applicable only to the present study sample. Finally, deriving and evaluating the LMR cutoff in the same cohort may have resulted in optimistic performance estimates, and the cutoff requires validation in larger, independent patient populations.

CONCLUSION

A lower LMR and a higher platelet count at admission were independently associated with surgically confirmed hollow viscus injury in this selected cohort of patients who underwent surgery for abdominal or thoracoabdominal stab wounds. The moderate discriminative performance of LMR indicates that it is

insufficient to confirm or exclude hollow viscus injury when used alone. LMR may be considered a low-cost and readily available adjunct to clinical examination and imaging findings. However, the findings and the identified cutoff value should be validated in larger, multicenter, independent cohorts before clinical implementation.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (No: 2024-01-31, Date: 22/01/2024).

Informed Consent: Written informed consent was obtained from all individual participants included in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – NS, TD, AS; Design – NS, MSD; Supervision – NS, FTO; Fundings – NS, SB; Materials – NS, AM; Data collection &/or processing – NS, AM; Analysis and/or interpretation – NS, AS; Literature search – NS, FTO, SB; Writing – NS, MSD; Critical review – NS, TD, AS.

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Clinical And Radiological Outcomes of Three Fixation Techniques For Isolated Greater Tuberosity Fractures

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ABSTRACT

Objective: The objective of the study was to compare the clinical and radiological outcomes of anatomical plate fixation, open reduction with cannulated screw fixation, and percutaneous cannulated screw fixation in patients with isolated greater tuberosity fractures of the proximal humerus.

Materials and Methods: A retrospective comparative study was conducted on 36 patients who underwent surgical treatment for isolated greater tuberosity fractures. Patients were divided into three groups according to the fixation technique: Plate fixation (n=12), open cannulated screw fixation (n=14), and percutaneous cannulated screw fixation (n=10). Functional outcomes were evaluated using the Constant-Murley score, pain using the visual analog scale (VAS), and shoulder range of motion measurements. Radiological outcomes and complications were also assessed.

Results: The mean Constant score was significantly higher in the open cannulated screw fixation group compared with the plate fixation and percutaneous screw fixation groups (89.0 ± 2.9 vs. 80.7 ± 5.7 and 78.6 ± 4.1 , respectively; $p < 0.001$). Patients treated with open screw fixation demonstrated significantly greater forward flexion, abduction, external rotation, and internal rotation. No significant differences were observed among the groups regarding VAS scores ($p = 0.602$). Complication rates were comparable among the three groups.

Conclusion: All three fixation techniques provided satisfactory clinical and radiological outcomes in the treatment of isolated greater tuberosity fractures. However, open reduction with cannulated screw fixation was associated with superior functional outcomes and improved shoulder range of motion.

Keywords: Bone plates, Bone screws, Fracture fixation, Humeral fractures, Shoulder joint

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INTRODUCTION

Fractures of the proximal humerus represent one of the most frequently encountered injuries of the shoulder girdle in adults, accounting for approximately 5% of all fractures.^[1,2] Approximately 20% of proximal humeral fractures involve the greater tuberosity as an isolated injury.^[3] While proximal humerus fractures are predominantly observed in the elderly osteoporotic population following low-energy trauma, isolated greater tuberosity fractures are more frequently encountered in relatively younger adults.^[2,4] Because the greater tuberosity serves as the insertion site of the rotator cuff tendons, fractures involving this region may significantly affect shoulder biomechanics and function.^[5-7] Superior or posterior displacement of the fragment may result in subacromial impingement, restricted range of motion, and impaired shoulder function.^[8]

Most isolated greater tuberosity fractures can be successfully managed conservatively, and more than 80% of cases do not require surgical intervention.^[3,9] However, surgical treatment is generally recommended for fractures with displacement >5 mm.^[4,10,11] In athletes and manual laborers, some authors have advocated surgical intervention even for displacement exceeding 3 mm.^[9,12] The primary goals of treatment are to achieve anatomical reduction, provide stable fixation, and facilitate early rehabilitation.

Various surgical techniques have been described for the treatment of isolated greater tuberosity fractures, including open reduction and plate osteosynthesis, open reduction with cannulated screw fixation, percutaneous cannulated screw fixation, and arthroscopically assisted suture or screw techniques.^[7,13] The choice of surgical method is influenced by fracture morphology, fragment size, direction of displacement, bone quality, and patient-related factors. Although satisfactory clinical and radiological outcomes have been reported with different surgical techniques, each method has its own advantages and disadvantages.^[14] However, clinical studies directly comparing anatomical plate fixation, open reduction with cannulated screw fixation, and percutaneous cannulated screw fixation remain scarce.^[13-17] Therefore, the current level of evidence regarding the optimal fixation method for isolated greater tuberosity fractures remains insufficient.

This retrospective comparative study evaluated the clinical and radiological performance of three fixation strategies; anatomical plate fixation, open reduction with cannulated screw fixation, and percutaneous cannulated screw fixation in patients with isolated greater tuberosity fractures. We hypothesized that, although different fixation techniques may provide comparable union rates, they may differ with respect to functional outcomes and complication profiles.

MATERIALS AND METHODS

Institutional ethics committee approval was obtained from the Health Sciences University Şişli Hamidiye Etfal Teaching and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee before data collection (approval date/number: March 31, 2026/3434), and the study was conducted in accordance with the Declaration of Helsinki.

This study was designed as a retrospective, single-center, comparative observational study.

Medical records and radiographic images of patients who underwent surgical treatment for isolated greater tuberosity fractures between January 2015 and March 2024 were retrospectively reviewed.

Adult patients (≥ 18 years) who underwent surgical fixation, open cannulated screw fixation, or percutaneous cannulated screw fixation for isolated greater tuberosity fractures and had a minimum follow-up period of 12 months were included in the study.

Patients with concomitant surgical neck fractures, three- or four-part proximal humerus fractures, previous surgery involving the affected shoulder, pathological fractures, associated neurovascular injuries, concomitant rotator cuff repair, insufficient radiographic records, or incomplete clinical follow-up were excluded.

After screening according to predefined eligibility criteria, a total of 36 patients were enrolled in the study. Patients were divided into three groups according to the fixation method used:

- Plate fixation group ($n=12$)
- Open cannulated screw fixation group ($n=14$)
- Percutaneous cannulated screw fixation group ($n=10$) (Fig. 1).

Surgical treatment was indicated for isolated greater tuberosity fractures with displacement >5 mm. In overhead athletes and heavy manual workers, surgical fixation was also indicated for fractures with displacement >3 mm.

Surgical Technique

Surgical treatment was carried out under general anesthesia in the beach-chair position by experienced shoulder surgeons. In the plate fixation group, fracture reduction was achieved through a deltoid-splitting approach followed by fixation with a proximal humeral locking plate. In the open cannulated screw fixation group, fracture reduction was performed through a limited open approach and stabilized using partially

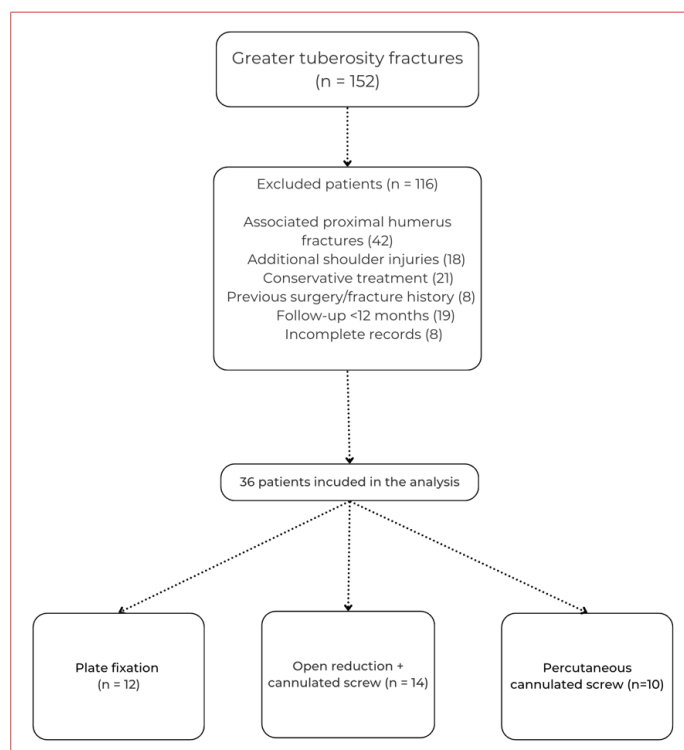


Figure 1. Patient selection flow chart.

threaded cannulated screws. In the percutaneous cannulated screw fixation group, closed or minimally invasive reduction was achieved under fluoroscopic guidance followed by percutaneous cannulated screw fixation.

Postoperatively, all patients followed the same rehabilitation protocol. Elbow, wrist, and hand range-of-motion exercises were initiated on the first post-operative day, while the shoulder was immobilized in a sling for 6 weeks. Pendulum and passive shoulder range-of-motion exercises were initiated after 3 weeks. Active-assisted and active range-of-motion exercises were started after 6 weeks, followed by strengthening exercises at 8–12 weeks. Patients were allowed to return to unrestricted daily activities after 3 months and to sports activities after 6 months.

Clinical Evaluation

Demographic variables including age, sex, injured side, dominant extremity involvement, mechanism of injury, and duration of follow-up were recorded. Functional assessment included the Constant–Murley score, while pain was evaluated using the visual analog scale (VAS). At the final follow-up visit, shoulder range of motion was evaluated, including forward flexion, abduction, external rotation, and internal rotation.

Radiological evaluation

Pre-operative computed tomography (CT) scans and plain radiographs were retrospectively reviewed. Fractures were classified according to the Mutch classification. Fragment displacement was measured on pre-operative CT images as the maximum displacement of the greater tuberosity fragment.

Standard anteroposterior shoulder radiographs obtained preoperatively, immediately postoperatively, and during routine follow-up visits were reviewed. Radiological assessment included fracture union, time to union, reduction loss, secondary displacement, and implant-related complications.

Fracture union was defined as the presence of bridging trabeculation across the fracture site on radiographs together with the absence of clinical tenderness at the fracture site. Time to union was recorded as the interval between surgery and radiographic evidence of fracture healing.

Reduction loss was defined as any deterioration in fracture reduction observed on follow-up radiographs compared with the immediate post-operative radiographs. Secondary displacement was defined as any post-operative displacement of the fracture fragment detected during follow-up. Radiographic evaluations were performed by reviewing the patients' follow-up radiographs and medical records.

Outcome Measures

The primary outcome measures were functional outcomes assessed by the Constant–Murley Score at final follow-up. Secondary outcome measures included VAS score, shoulder range of motion, time to union, reduction loss, secondary displacement, reoperation, and implant-related complications.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables as frequency and percentage.

The normality of data distribution was assessed using the Shapiro–Wilk test. Homogeneity of variances was evaluated using Levene's test. Comparisons of continuous variables among the three treatment groups were performed using one-way analysis of variance for normally distributed data. When a significant overall difference was detected, pairwise comparisons were conducted using Tukey's honestly significant difference test. Because VAS scores did not demonstrate normal distribution, comparisons among groups were performed using the Kruskal–Wallis test.

Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. For all analyses, a two-tailed $p < 0.05$ was considered statistically significant. In addition to p -values, 95% confidence intervals (95% CIs) were reported for key continuous outcome measures.

RESULTS

A total of 36 patients were included in the study, comprising 12 patients treated with plate fixation, 14 patients treated with open reduction screw fixation, and 10 patients treated with percutaneous screw fixation. All fractures were classified as Type II (split-type). The mean pre-operative fragment displacement was 7.8 ± 2.1 mm (range, 3.5–12.4 mm), and all fractures demonstrated superior displacement of the greater tuberosity fragment. The mean age was 53.9 ± 9.3 years in the plate group, 51.8 ± 9.1 years in the open reduction screw group, and 50.1 ± 7.8 years in the percutaneous screw group. Mean follow-up duration was 43.7 ± 12.0 months, 40.3 ± 10.3 months, and 41.6 ± 7.9 months, respectively. Baseline demographic and clinical variables were comparable across treatment groups regarding age, sex, diabetes mellitus, smoking status, trauma mechanism, follow-up duration, or time from injury to surgery (all $p > 0.05$). However, operative time differed significantly among the groups ($p < 0.001$), with the percutaneous cannulated screw fixation group demonstrating the shortest mean operative time (115.1 ± 18.4 min) compared with the plate fixation (157.5 ± 10.2 min) and open cannulated screw fixation groups (152.7 ± 16.8 min). Baseline demographic and clinical characteristics are presented in Table 1.

At final follow-up, the mean VAS score was 0.67 ± 0.65 in the plate group, 0.57 ± 0.51 in the open reduction screw group, and 0.40 ± 0.52 in the percutaneous screw group. No statistically significant difference was observed among the groups ($p = 0.602$).

The mean Constant score was 80.7 ± 5.7 (95% CI, 77.1–84.4) in the plate group, 89.0 ± 2.9 (95% CI, 87.4–90.7) in the open reduction screw group, and 78.6 ± 4.1 (95% CI, 75.7–81.5) in the percutaneous screw group. Group comparisons demonstrated a significant effect among the groups ($p < 0.001$) (Fig. 2).

Mean forward flexion was $143.75 \pm 9.80^\circ$ (95% CI, 137.52–149.98°) in the plate group, $151.07 \pm 7.89^\circ$ (95% CI, 146.52–155.63°) in the open reduction screw group, and $142.00 \pm 10.33^\circ$ (95% CI, 134.61–149.39°) in the percutaneous screw group. The overall comparison demonstrated a statistically significant difference ($p = 0.046$).

Mean abduction was $139.17 \pm 7.64^\circ$ (95% CI, 134.31–144.02°) in the plate group, $148.57 \pm 11.17^\circ$ (95% CI, 142.12–155.02°) in the open reduction screw group, and $137.00 \pm 6.75^\circ$ (95%

Table 1. Baseline demographic and clinical characteristics of the study groups

Variable	Plate (n=12)	Open screw (n=14)	Percutaneous screw (n=10)
Age (years)	53.9 ± 9.3	51.79 ± 9.1	50.10 ± 7.79
Follow-up duration (months)	43.7 ± 12.0	40.3 ± 10.3	41.6 ± 7.9
Gender, n (%)			
Male	6 (50.0)	6 (42.9)	6 (60.0)
Female	6 (50.0)	8 (57.1)	4 (40.0)
Diabetes mellitus, n (%)			
Yes	2 (16.7)	4 (28.6)	2 (20.0)
No	10 (83.3)	10 (71.4)	8 (80.0)
Smoking, n (%)			
Yes	7 (58.3)	9 (64.3)	7 (70.0)
No	5 (41.7)	5 (35.7)	3 (30.0)
Trauma type, n (%)			
High-energy	2 (16.7)	2 (14.3)	2 (20.0)
Low-energy	10 (83.3)	12 (85.7)	8 (80.0)
Time from injury to surgery (days)	2.08 ± 0.79	1.86 ± 0.86	1.60 ± 0.70
Operation time (minutes)	157.5 ± 10.2	152.7 ± 16.8	115.1 ± 18.4

Data are presented as mean $\pm$ SD or n (%)

CI, 132.17–141.83°) in the percutaneous screw group. A statistically significant difference was identified among the groups ($p = 0.007$).

Mean external rotation was $57.08 \pm 7.22^\circ$ (95% CI, 52.50–61.67°) in the plate group, $64.29 \pm 6.75^\circ$ (95% CI, 60.39–68.18°) in the open reduction screw group, and $55.50 \pm 9.27^\circ$ (95% CI, 48.87–62.13°) in the percutaneous screw group. The overall comparison was statistically significant ($p = 0.016$).

Mean internal rotation was $49.58 \pm 4.98^\circ$ (95% CI, 46.42–52.75°) in the plate group, $55.71 \pm 6.16^\circ$ (95% CI, 52.16–59.27°) in the open reduction screw group, and $49.50 \pm 3.69^\circ$ (95% CI, 46.86–52.14°) in the percutaneous screw group. A statistically significant difference was observed among the groups ($p = 0.006$). Detailed clinical outcome data are presented in Table 2.

Fracture healing was confirmed radiographically in every patient. No cases of non-union or additional secondary displacement were observed during follow-up. Complications occurred in 3 patients (25.0%) in the plate fixation Group, 2

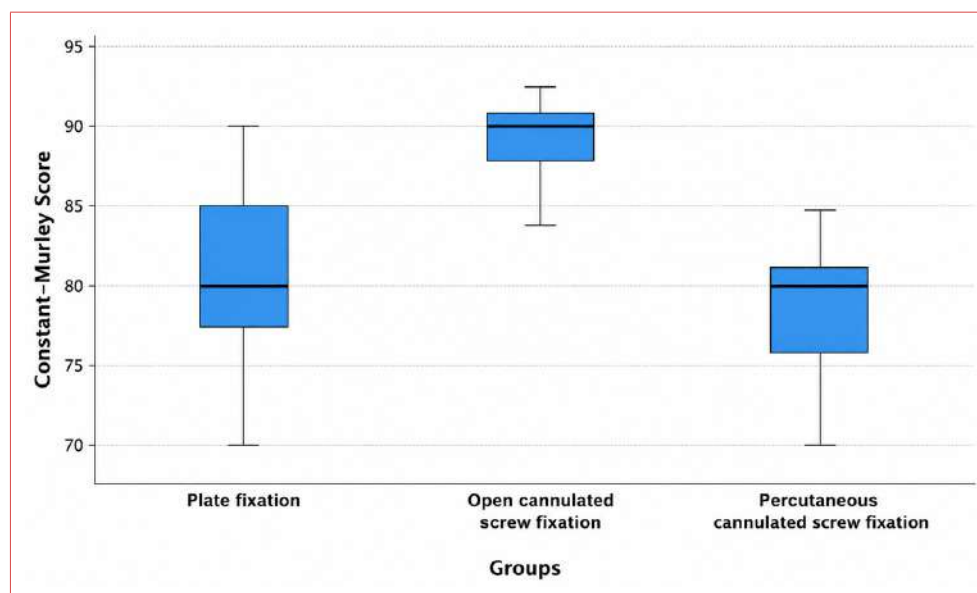


Figure 2. Box plot showing the distribution of Constant-Murley scores among the three fixation groups. Patients treated with open reduction and cannulated screw fixation demonstrated higher functional scores than those treated with plate fixation or percutaneous screw fixation.

patients (14.3%) in the open reduction screw fixation group, and 3 patients (30.0%) in the percutaneous screw fixation group. There was no statistically significant difference in the overall complication rates among the three groups ($p=0.633$). In the plate group, complications included two infections and one case of shoulder stiffness. In the open reduction screw fixation group, two cases of loss of reduction were observed. In the percutaneous screw fixation group, three cases of screw back-out occurred. Reoperation was performed in all patients with complications, including debridement for infection, manipulation under anesthesia for shoulder stiffness, revision surgery for loss of reduction, and implant removal for screw back-out (Table 3).

DISCUSSION

There is still no consensus regarding the optimal surgical treatment for isolated greater tuberosity fractures. The principal observation of the present study was that patients treated with open reduction and cannulated screw fixation achieved higher Constant scores and better shoulder range of motion compared with those treated with anatomical plate fixation or percutaneous cannulated screw fixation. In contrast, no substantial differences were observed among the groups in terms of pain levels, union rates, or complication profiles. These findings suggest that all three techniques can provide acceptable clinical and radiological outcomes, whereas open reduction with cannulated screw fixation may offer certain advantages with respect to functional recovery.

Table 2. Comparison of clinical outcomes between fixation groups

Variable	Plate (n=12)	Open screw (n=14)	Percutaneous screw (n=10)	p
VAS score	0.67±0.65	0.57±0.51	0.40±0.52	0.602 [†]
Constant score	80.7±5.7	89.0±2.9	78.6±4.1	<0.001
Forward flexion (°)	143.75±9.80	151.07±7.89	142.00±10.33	0.046
Abduction (°)	139.17±7.64	148.57±11.17	137.00±6.75	0.007
External rotation (°)	57.08±7.22	64.29±6.75	55.50±9.27	0.016
Internal rotation (°)	49.5±4.9	55.71±6.16	49.50±3.69	0.006

Data are presented as mean±standard deviation. VAS: Visual Analog Scale, ANOVA: Analysis of variance. [†]Kruskal–Wallis test; all other comparisons performed using one-way ANOVA

Table 3. Radiological outcomes, implant-related complications, and reoperations

Variable	Plate (n=12)	Open screw (n=14)	percutaneous Screw (n=10)	p
Infection, n (%)	2 (16.7)	0	0	
Shoulder stiffness, n (%)	1 (8.3)	0	0	
Loss of reduction, n (%)	0	2 (14.3)	0	
Screw back-out, n (%)	0	0	3 (30.0)	
Reoperation, n (%)	3 (25.0)	2 (14.3)	3 (30.0)	
Fracture union, n (%)	12 (100)	14 (100%)	10 (100)	
Overall complication, n (%)	3 (25.0)	2 (14.3)	3 (30.0)	0.633

Data are presented as n (%). Overall complication rates were compared using Pearson's Chi-square test

Previous studies have demonstrated favorable outcomes with various surgical techniques for isolated greater tuberosity fractures.^[10,13,16-19] Tao et al.,^[6] in their study comparing three different plate-based fixation techniques, reported satisfactory clinical outcomes across all groups. Similarly, Choi et al.^[7] demonstrated high union rates and good functional outcomes in patients treated with low-profile locking plates. In a systematic review, Levy et al.^[19] concluded that although fixation techniques generally provide satisfactory outcomes, plate-based fixation may result in greater construct stiffness and an increased risk of post-operative motion restriction compared with screw fixation. Studies have also shown that plate fixation, screw fixation, and arthroscopic techniques can provide satisfactory results when used with appropriate indications.^[11,16,20,21] Consistent with these findings, all three groups in the present study achieved low pain scores and acceptable functional outcomes.

In the current study, patients treated with open reduction and cannulated screw fixation exhibited superior Constant scores and better range of motion compared with the other groups. One possible explanation is that open reduction allows more reliable restoration of anatomical alignment, while cannulated screw fixation provides adequate stability with less implant bulk. Although anatomical plates offer the advantage of rigid fixation, particularly in comminuted fractures, they require more extensive soft-tissue dissection and greater implant volume, which may adversely affect post-operative shoulder motion in some patients. On the other hand, previous studies have reported favorable clinical outcomes with percutaneous screw fixation, highlighting the advantages of a minimally invasive approach and lower soft-tissue morbidity. Furthermore, previous biomechanical and clinical studies have shown that cannulated screw fixation provides biomechanical stability comparable to, or greater than, that of other commonly used fixation methods.^[11,14,22-24] Therefore, the superior functional outcomes observed in the

open reduction and cannulated screw fixation group in the present study are unlikely to be explained solely by differences in fixation strength. More accurate restoration of anatomical reduction achieved through direct visualization during open reduction may have contributed to these findings.

Another notable finding was the significantly shorter operative time in the percutaneous cannulated screw fixation group. In our study, the operative time in the percutaneous cannulated screw fixation group was found to be significantly shorter than in the other groups. This finding can be explained by the minimally invasive nature of the percutaneous approach, which requires less soft-tissue dissection and less surgical exposure. Previous studies have also reported that minimally invasive or percutaneous techniques can shorten operative time and reduce soft-tissue damage.^[25] However, in our study, this perioperative advantage did not translate into superior functional outcomes. Therefore, operative time alone should not be the sole determining factor in the selection of a surgical method; fracture morphology, the achievement of stable fixation, and expected functional outcomes must be evaluated together.

Complication rates were relatively low in all three groups. Infections and shoulder stiffness were observed in the plate fixation group, loss of reduction occurred in the open reduction screw fixation group, and screw back-out was encountered in the percutaneous screw fixation group. Nevertheless, no substantial differences in complication rates were identified among the groups. Overall, the complication profile observed in the present study was consistent with those reported in previous studies. In particular, screw back-out and loss of reduction are recognized complications of cannulated screw fixation, whereas infection and post-operative stiffness have been reported following open surgical procedures.^[5,11,15,19,20,24]

Because fracture morphology plays an important role in treatment selection, only Mutch Type II (split-type) fractures were included in this study. This fracture pattern generally provides

sufficient bone stock for different fixation strategies, including plate fixation and cannulated screw fixation, allowing a more homogeneous comparison of the evaluated osteosynthesis techniques.^[12,13,15,23,25] Although several fixation methods have been described for Mutch Type II fractures, direct comparisons between open and percutaneous cannulated screw fixation remain limited. Therefore, our findings should be interpreted primarily in the context of Mutch Type II fractures and may not be directly generalizable to other fracture patterns.

This study has several strengths. To the best of our knowledge, studies directly comparing anatomical plate fixation, open reduction with cannulated screw fixation, and percutaneous cannulated screw fixation are scarce. In addition, all patients were treated at a single institution and followed according to a similar post-operative protocol, thereby reducing heterogeneity among the groups. Furthermore, the inclusion of both clinical and radiological outcomes, as well as complication profiles, enhances the comprehensiveness of the study.

Limitations

Certain limitations should be taken into account when interpreting the results. First, the retrospective design introduces the possibility of selection bias. Second, no a priori sample size or power calculation was performed because of the retrospective design of the study. Therefore, the relatively small sample size may have limited the statistical power, particularly for detecting differences in infrequent outcomes such as post-operative complications. Accordingly, non-significant differences in complication rates should be interpreted with caution. Third, because the choice of surgical technique was based on surgeon preference rather than randomization, the possibility of selection bias and residual confounding cannot be excluded.

CONCLUSION

Overall, anatomical plate fixation, open reduction with cannulated screw fixation, and percutaneous cannulated screw fixation all provided satisfactory clinical and radiological outcomes in the treatment of isolated greater tuberosity fractures. However, patients treated with open reduction and cannulated screw fixation achieved higher Constant scores and better shoulder range of motion. Larger prospective comparative studies are warranted to further clarify the optimal fixation strategy for isolated greater tuberosity fractures.

DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Health Sciences University Şişli Hamidiye Etfal Teaching and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee (No: 3434 Date: 31/03/2026).

Informed Consent: Informed consent was obtained from all patients involved in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – YA, OTE; Design – YA, OTE, MAB; Supervision – OTE; Resources – OTE; Materials – EI, IK, MM; Data collection &/or processing – YA, MAB, OTE; Analysis and/or interpretation – YA, MAB, OTE; Literature search – YA, MAB; Writing – YA; Critical review – MAB, EI, IK, MM, OTE.

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Remission in Graves' Disease: Predictive Value of Biochemical And Systemic Inflammatory Indices – A Single-Center Retrospective Cohort Study

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ABSTRACT

Objective: This study addresses the association of hematological inflammatory indices with remission in patients with Graves' disease (GD) and their potential contribution as remission-related markers.

Materials and Methods: This retrospective cohort study was conducted at a single tertiary endocrinology center. The study cohort consisted of 78 adults with GD who were admitted to a tertiary endocrinology clinic from September 2022 to September 2023. Demographic, clinical, and laboratory data, including thyroid function tests and thyrotropin receptor antibody (TRAb) levels, were collected. Indices reflecting systemic inflammation, namely, aggregate index of systemic inflammation, systemic inflammation response index, systemic immune-inflammation index, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, were calculated using complete blood count parameters. Remission was defined as achieving clinical and biochemical euthyroidism following 12–18 months of continuous antithyroid drug therapy, maintained without relapse for at least 12 months after treatment discontinuation. Subjects were stratified by remission status, and six separate binary logistic regression models were constructed, each including TRAb, age, and sex as core covariates alongside one inflammatory index, to avoid quasi-complete separation arising from a low events-per-variable ratio.

Results: Remission was achieved in 44.9% of patients. Baseline T3, T4, and TRAb levels were significantly elevated in patients without remission (all $p < 0.001$). Age, sex, and inflammatory indices were comparable between groups (all $p > 0.05$). In all six logistic regression models, TRAb was the only independent predictor of non-remission (Odds ratio: 1.267, 95% confidence interval [CI]: 1.144–1.403, $p < 0.001$ across models), while no inflammatory index achieved statistical significance. Receiver operating characteristic analysis demonstrated excellent discriminatory performance for TRAb (area under the curve = 0.897, 95% CI: 0.824–0.971, $p < 0.001$), with a cohort-derived cut-off of 13.6 IU/L (sensitivity 91.4%, specificity 83.7%). This cut-off should be regarded as exploratory because it was derived from a small, single-center cohort without external validation.

Conclusion: TRAb is the most reliable predictor of remission in GD, whereas hematological inflammatory indices do not appear to have significant predictive value. These findings highlight the limited clinical utility of non-specific inflammatory markers and reinforce the importance of disease-specific autoantibodies in determining prognosis.

Keywords: Antithyroid drugs, graves' disease, hyperthyroidism, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index

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INTRODUCTION

As an autoimmune condition, Graves' disease (GD) is the leading cause of endogenous hyperthyroidism, driven by thyrotropin receptor antibody (TRAb) that stimulates the thyroid-stimulating hormone receptor and increases thyroid hormone production.^[1-3]

Therapeutic options involve antithyroid medications to reduce hormone synthesis, in addition to permanent treatment modalities, including radioactive iodine administration and thyroidectomy.^[4] Even though antithyroid medications are the preferred initial approach, disease recurrence following discontinuation continues to represent a major clinical problem, with rates of up to 50–60%.^[5,6] Therefore, identifying reliable predictors of remission and relapse remains an important clinical challenge.

Recently, easily accessible and cost-effective inflammatory indices based on blood counts (neutrophil-to-lymphocyte ratio [NLR], monocyte-to-lymphocyte ratio [MLR], platelet-to-lymphocyte ratio [PLR], systemic immune-inflammation index [SII], systemic inflammation response index [SIRI], aggregate index of systemic inflammation [AISI]) have been investigated in various inflammatory and metabolic diseases. However, studies evaluating their role in GD have yielded inconsistent and controversial results.^[7-9] The inconsistency in prior findings may be attributable to heterogeneous study populations, small sample sizes, differences in disease activity at the time of blood sampling, variability in antithyroid drug (ATD) dosing, and whether indices were measured at diagnosis or during follow-up. Our study contributes to the literature by systematically evaluating multiple hematological inflammatory indices in a well-characterized cohort of GD patients, using multivariate analysis to control for confounders, with remission as the primary outcome.

We hypothesized that elevated hematological inflammatory indices at baseline would be associated with a lower likelihood of achieving remission in GD patients treated with ATD. The primary aim of this study was to evaluate whether hematological inflammatory indices (NLR, MLR, PLR, SII, SIRI, and AISI) are independent predictors of remission in GD, and to assess the comparative predictive utility of these markers alongside TRAb and thyroid hormone levels.

MATERIALS AND METHODS

This retrospective, single-center cohort study was conducted at Endocrinology Department of Prof. Dr. Cemil Tascioglu City Hospital, Hospital using data from the hospital electronic medical record system. Patients were identified using the International Classification of Diseases, 10th Revision (ICD-10) code E05.0 who were admitted between September 2022 and

September 2023. A total of 322 patients were initially identified using the ICD-10 code E05.0. After applying the exclusion criteria, 244 patients were excluded due to pregnancy (n=42), insufficient follow-up data (n=114), acute or chronic infections (n=24), hematological or rheumatological diseases (n=18), history of malignancy (n=34), and chronic renal failure (n=12). Consequently, 78 patients aged ≥ 18 years with a diagnosis of GD and complete medical records were included in the final analysis. (Fig. 1) No patients were lost to follow-up, as the study was retrospective and data were extracted from complete electronic medical records. Patients were diagnosed with GD between January 2019 and August 2022. Medical records were reviewed retrospectively between September 2022 and September 30, 2023 (data cut-off date). Total follow-up duration was calculated from the date of initial GD diagnosis to the date of the last recorded clinical visit or the data cut-off date, whichever occurred first.

Demographic characteristics (age and sex), biochemical parameters including thyroid-stimulating hormone (TSH), free thyroxine (T4), triiodothyronine (T3), and TRAb, as well as ATD treatment duration and total follow-up duration (from diagnosis to the last recorded clinical visit) were recorded.

Systemic inflammatory indices calculation was based on:

- $AISI = (\text{neutrophil} \times \text{monocyte} \times \text{platelet}) / \text{lymphocyte}$
- $SIRI = (\text{neutrophil} \times \text{monocyte}) / \text{lymphocyte}$
- $SII = (\text{platelet} \times \text{neutrophil}) / \text{lymphocyte}$
- $PLR = \text{platelet count} / \text{lymphocyte count}$
- $NLR = \text{neutrophil count} / \text{lymphocyte count}$
- $MLR = \text{monocyte count} / \text{lymphocyte count}$.

Hematological inflammatory indices were calculated using complete blood count parameters obtained at the time of initial diagnosis, before initiation of ATD therapy, to avoid confounding effects of ATD-related hematological changes such as leukopenia.

The diagnosis of GD was based on clinical findings of thyrotoxicosis together with biochemical evidence of hyperthyroidism, including suppressed TSH, elevated free T4 and/or T3 levels, accompanied by positive TRAb. Diagnosis was further supported by increased thyroid uptake on ^{99m}Tc-pertechnetate scintigraphy and/or ultrasonographic findings consistent with diffuse thyroid enlargement and increased vascularity.

Remission was defined according to clinical guidelines as the achievement of clinical and biochemical euthyroidism (normal TSH, free T4, and T3 levels) following 12–18 months

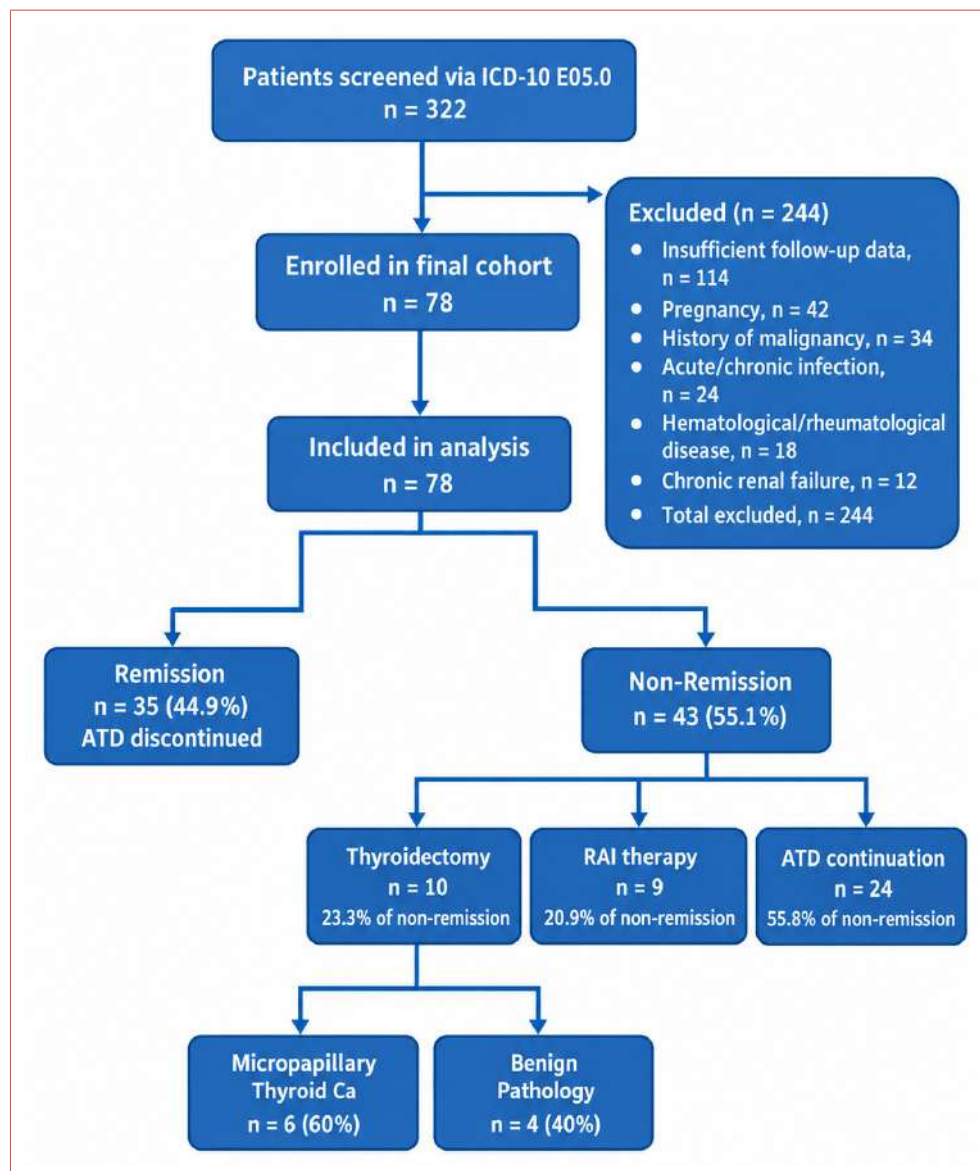


Figure 1. STROBE flow diagram. STROBE flow diagram illustrating patient screening, exclusion, and allocation. A total of 322 patients were initially identified using ICD-10 code E05.0. After applying exclusion criteria (n=244), 78 patients were included in the final analysis. Non-remission patients were further categorized by treatment modality. All papillary thyroid carcinomas identified in the thyroidectomy group were micropapillary (≤ 1 cm) incidental findings. ATD: Antithyroid drug; RAI: Radioactive iodine; Ca: Carcinoma

of continuous ATD therapy, maintained without relapse for at least 12 months after treatment discontinuation. Relapse was defined as recurrence of biochemical or clinical hyperthyroidism within the post-discontinuation follow-up period. All patients were treated with methimazole (MMI) as the first-line ATD, in accordance with guideline recommendations. Propylthiouracil was used only in cases

of MMI intolerance or specific contraindications (e.g., first trimester of pregnancy), which were excluded from this study. Treatment was discontinued when patients achieved biochemical euthyroidism on the lowest effective MMI dose (typically ≤ 5 mg/day). TRAb negativity at the time of treatment discontinuation was additionally documented when available.

Patients were divided into remission and non-remission groups. Patients were classified as non-remission if they: (1) required ongoing ATD therapy (MMI >5 mg/day) beyond 24 months without achieving biochemical euthyroidism; (2) experienced disease relapse (recurrent hyperthyroidism) after initial ATD discontinuation; or (3) required definitive therapy (radioactive iodine or thyroidectomy) at any point during follow-up due to treatment failure or patient preference guided by shared decision-making.

TRAb levels were measured using the electrochemiluminescence immunoassay method (Elecsys Anti-TSHR assay, Roche Diagnostics), with a reference range of <1.75 IU/L.

Patients with pregnancy, insufficient follow-up data, or comorbid conditions known to influence hematological parameters, including acute or chronic infections, hematological or rheumatological diseases, a history of malignancy, and chronic renal failure, were excluded from the study.

To minimize selection bias, all consecutive patients meeting the inclusion criteria during the study period were enrolled without further selection. Standardized definitions for remission and non-remission were applied uniformly. Data were extracted from the structured electronic medical record system using predefined variables. Laboratory measurements were performed at the same certified central laboratory throughout the follow-up period.

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation, whereas categorical variables are expressed as counts and percentages. Group differences were evaluated using either the independent samples t-test or the Mann–Whitney U test, depending on data distribution (assessed using the Shapiro–Wilk test). The Chi-square test was employed for categorical comparisons. Due to the low events-per-variable ratio (EPV) (EPV=35/11=3.2, below the recommended minimum of 10), simultaneous entry of all candidate variables was not appropriate. Therefore, six separate binary logistic regression models were constructed, each including TRAb, age, and sex as core covariates alongside one inflammatory index (NLR, MLR, PLR, SII, SIRI, or AISI). This strategy was used to limit model overparameterization. However, given the small sample size and limited number of events, estimates for some inflammatory indices were imprecise, as reflected by wide confidence intervals (CI). Results are expressed as odds ratios (OR) with 95% CI. For all binary logistic regression models, non-remission was coded as 1 and remission as 0; therefore, ORs >1 indicate higher odds

of non-remission. Receiver operating characteristic (ROC) curve analysis was performed for TRAb and other significant continuous predictors to determine optimal diagnostic cut-off values using the Youden index. Statistical significance was defined as $p<0.05$.

The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital (approval date: September 26, 2023; decision number: 184), and the study adhered to the Declaration of Helsinki.

RESULTS

Baseline Characteristics

Seventy-eight individuals were incorporated into the study cohort. The mean age was 40.4 ± 11.4 years. The cohort was predominantly female (82.1%). The mean ATD treatment duration was 30.1 ± 11.7 months (range: 8–59 months). The enrollment period (September 2022–September 2023) refers to the data extraction period; patients diagnosed at earlier time points were included if follow-up data were available within this period. The data cut-off was September 30, 2023. The mean total follow-up duration (from diagnosis to last recorded visit, including the post-treatment observation period) was 45.4 ± 12.1 months (remission group: 44.2 ± 8.2 months; non-remission group: 46.4 ± 14.9 months; $P=0.395$). Baseline laboratory values included mean T4 of 28.9 ± 11.3 pmol/L, T3 of 10.6 ± 5.6 pmol/L, and TRAb of 15.9 ± 11.4 IU/L (Table 1).

Remission Rates

Remission was achieved in 35 patients (44.9%), whereas 43 patients (55.1%) did not achieve remission. In the non-remission group, 79.1% of patients were female, while 20.9% were male. Radioactive iodine (RAI) therapy was administered in 20.9% of non-remission patients, and 23.3% underwent surgical treatment. Among surgically treated patients, 60% had papillary thyroid carcinoma (PTC) (all micropapillary, ≤ 1 cm, identified as incidental findings on pathological examination; no preoperative nodules were identified on ultrasonography) and 40% had benign pathology.

The non-remission group had significantly higher T4 levels (33.0 ± 12.7 vs. 23.9 ± 6.4 pmol/L, $p<0.001$). Similarly, T3 levels were elevated (12.7 ± 6.5 vs. 8.1 ± 2.8 pmol/L, $p<0.001$), and TRAb levels were substantially higher (22.9 ± 9.9 vs. 7.2 ± 6.1 IU/L, $p<0.001$).

There were no significant differences between groups in terms of age ($p=0.474$), sex distribution ($p=0.453$), or TSH levels ($p=1.00$). There were no significant differences in systemic inflammatory indices between patients who achieved remission and those who did not (all $p>0.05$). The

Table 1. Baseline characteristics and group comparisons

Variable	Overall (n=78)	No remission (n=43)	Remission (n=35)	p
Age (years)	40.4±11.4	39.6±12.3	41.4±10.4	0.474
Sex (female) (%)	82.1	79.1	85.7	0.453
TSH (mIU/L)	0.01±0.00	0.01±0.00	0.01±0.00	1.00
T4 (pmol/L)	28.9±11.3	33.0±12.7	23.9±6.4	<0.001
T3 (pmol/L)	10.6±5.6	12.7±6.5	8.1±2.8	<0.001
TRAb (IU/L)	15.9±11.4	22.9±9.9	7.2±6.1	<0.001
NLR	1.63±0.58	1.57±0.56	1.71±0.60	0.308
MLR	0.21±0.07	0.21±0.07	0.22±0.08	0.455
PLR	122.3±41.7	122.9±42.3	121.6±41.2	0.892
SII	454.7±195.2	442.3±177.8	468.9±212.6	0.557
SIRI	0.81±0.41	0.77±0.36	0.87±0.46	0.300
AISI	229.3±137.5	217.6±110.4	243.3±163.3	0.430
ATD treatment duration (months)	30.1±11.7	35.5±12.5	23.4±5.6	<0.001
Total follow-up duration (months)	45.4±12.1	46.4±14.9	44.2±8.2	0.395

Data are presented as mean±standard deviation or percentages. P-values calculated using an independent-samples *t*-test or Mann–Whitney U test, where appropriate. ATD: Antithyroid drug; TRAb: Thyrotropin receptor antibody; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; AISI: Aggregate index of systemic inflammation

non-remission group had a significantly longer ATD treatment duration than those in remission (35.5±12.5 vs. 23.4±5.6 months, *p*<0.001). Total follow-up duration was comparable between groups (non-remission: 46.4±14.9 months vs. remission: 44.2±8.2 months, *p*=0.395).

Multivariable Logistic Regression Analysis

Six separate logistic regression models were constructed as described in the Methods. In all models, non-remission was the dependent variable (coded as 1). Across all models, TRAb

Table 2. Multivariable logistic regression – six separate models (n=78)

Model	Index	TRAb OR (95% CI)	TRAb p	Age OR (95% CI)	Sex OR (95% CI)	Index OR (95% CI)/p
1	NLR	1.267 (1.144–1.403)	<0.001	1.045 (0.976–1.118)	2.156 (0.381–12.203)	0.624 (0.192–2.028)/ <i>P</i> =0.433
2	MLR	1.268 (1.144–1.405)	<0.001	1.045 (0.976–1.118)	2.411 (0.450–12.909)	0.679 (0.000–9647)/ <i>P</i> =0.937
3	PLR	1.268 (1.145–1.404)	<0.001	1.044 (0.976–1.117)	2.581 (0.427–15.606)	1.002 (0.985–1.018)/ <i>P</i> =0.848
4	SII	1.267 (1.144–1.404)	<0.001	1.046 (0.977–1.119)	2.279 (0.401–12.954)	1.000 (0.996–1.003)/ <i>P</i> =0.778
5	SIRI	1.265 (1.142–1.401)	<0.001	1.044 (0.976–1.117)	2.428 (0.447–13.190)	0.695 (0.123–3.911)/ <i>P</i> =0.679
6	AISI	1.267 (1.144–1.404)	<0.001	1.045 (0.977–1.118)	2.384 (0.440–12.914)	1.000 (0.995–1.004)/ <i>P</i> =0.877

The dependent variable was coded as non-remission=1 and remission=0. Accordingly, OR>1 indicates increased odds of non-remission, whereas OR<1 indicates decreased odds of non-remission. Each model included TRAb, age, sex, and one inflammatory index. All TRAb *p*<0.001. OR: Odds ratio; CI: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; AISI: Aggregate index of systemic inflammation

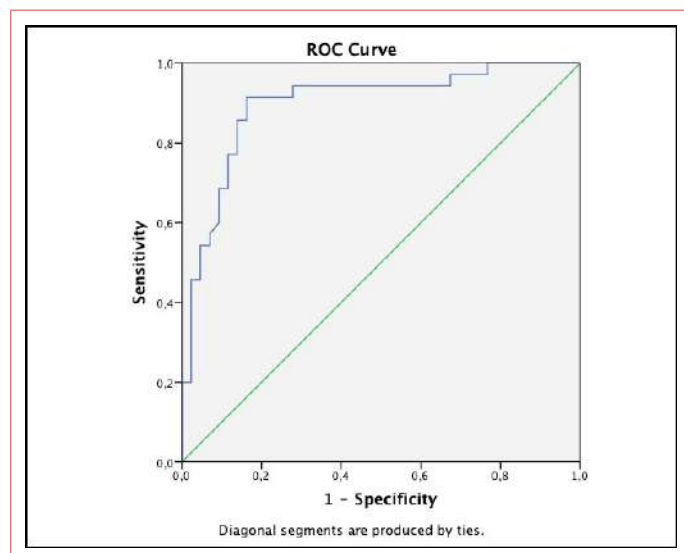


Figure 2. ROC curve for TRAb in predicting remission in Graves' disease. Receiver operating characteristic (ROC) curve for TRAb in predicting remission in patients with Graves' disease treated with antithyroid drugs. The area under the curve (AUC) was 0.897 (95% CI: 0.824–0.971, $p < 0.001$), indicating excellent discriminatory performance. The optimal cut-off value, determined by the Youden index, was 13.6 IU/L (sensitivity: 91.4%, specificity: 83.7%). The diagonal reference line represents chance-level discrimination (AUC=0.5). TRAb: Thyrotropin receptor antibody, CI: Confidence interval

was the only statistically significant independent predictor of non-remission (OR: 1.267, 95% CI: 1.144–1.403, $P < 0.001$ in all models). Each 1 IU/L increase in TRAb was associated with approximately 27% higher likelihood of non-remission. Age and sex were not significant in any model (all $p > 0.05$). None of the six inflammatory indices achieved statistical significance in any model (all $p > 0.05$). Full results are presented in Table 2.

In an exploratory ROC analysis, TRAb demonstrated excellent discriminatory ability for remission status (area under the curve=0.897, 95% CI: 0.824–0.971, $p < 0.001$) (Fig. 2). The Youden index identified 13.6 IU/L as the optimal cut-off within the present cohort, yielding a sensitivity of 91.4% and a specificity of 83.7% for predicting non-remission. Given the small, single-center sample and absence of external validation, this cut-off should be regarded as exploratory.

Sensitivity Analysis

To assess whether the surgical subgroup influenced the results, analyses were repeated after excluding the 10 surgically treated patients ($n=68$; remission $n=35$, non-remission $n=33$). TRAb remained the only significant independent predictor

across all six models (OR for non-remission: 1.258–1.261, 95% CI: 1.132–1.402, $p < 0.001$), while no inflammatory index achieved significance (all $p > 0.05$) (Suppl Table 1).

DISCUSSION

In the present study, we analyzed the biochemical and systemic inflammatory indices and remission status in patients with GD. Remission was achieved in 44.9% of patients. Higher baseline T3, T4, and TRAb levels were significantly associated with non-remission. Across the six multivariable models, TRAb was consistently associated with remission status, whereas none of the evaluated inflammatory indices reached statistical significance.

The predominance of female patients and the remission rate observed in our study are consistent with previous reports and current guidelines, indicating that approximately 40–50% of patients achieve remission following ATD therapy.^[6,10] Despite improvements in diagnostic approaches and treatment accessibility, relapse remains a major clinical challenge, underscoring the need for reliable predictors of disease course.

Our results further reinforce the key role of TRAb in the pathophysiology and prognosis of GD.^[11] TRAb stimulates the thyroid-stimulating hormone receptor, resulting in persistent hyperthyroidism, and has been consistently associated with disease activity and relapse risk. In our study, TRAb was the only independent predictor of remission, with every 1 IU/L increase associated with a 26% higher likelihood of non-remission (OR: 1.267, 95% CI: 1.144–1.403, $p < 0.001$). Exploratory ROC analysis demonstrated good discriminatory performance of baseline TRAb for remission status. A cut-off of 13.6 IU/L provided the optimal combination of sensitivity and specificity within our cohort. However, this threshold was derived from a relatively small, single-center population and was not externally validated. It should therefore be regarded as a hypothesis-generating finding rather than an established clinical threshold. Larger prospective studies with external validation are required before a specific TRAb cut-off can be incorporated into treatment decisions. These results are in line with earlier studies indicating that elevated TRAb levels are strongly associated with poor treatment response and increased relapse rates.^[12–14]

Baseline T3 and T4 levels were significantly higher in the non-remission group, indicating greater biochemical disease activity at presentation. However, T3 and T4 were not included in the revised multivariable regression models because the limited number of outcome events restricted the number of covariates that could be incorporated without overparameterization. Accordingly, no conclusions regarding their independent predictive value can be drawn from the present analysis.

In recent years, inflammatory indices have been investigated as potential prognostic markers in autoimmune and inflammatory diseases. However, their role in GD remains controversial. Some studies have suggested associations with disease activity or treatment response,^[7,8,15] while others have reported no significant relationship.^[9] Dasgupta et al.^[7] evaluated PLR as a novel surrogate marker to differentiate between patients with GD and subacute thyroiditis. Kim et al.^[15] reported that high NLR was associated with relapse in GD; however, this differs from our findings in that NLR was measured at treatment completion rather than at baseline, which may better reflect residual immune activity at that stage. Furthermore, their study focused on relapse after ATD withdrawal rather than overall remission status.

Furthermore, changes in hematological parameters following ATD treatment or differences between subgroups of thyrotoxicosis rather than GD alone were discussed in the literature^[16-19] these studies primarily focused on disease activity or treatment-related changes rather than remission outcomes. Studies evaluating inflammatory markers in thyroid eye disease, which represents a distinct inflammatory phenotype from uncomplicated GD, potentially explain the absence of associations in our cohort.^[8,20]

In our study, none of the evaluated inflammatory indices were independently associated with remission in multivariable analysis. This finding is consistent with studies reporting limited predictive value of these indices in hyperthyroid states.^[9] The absence of a relationship between systemic inflammatory indices and remission may be attributed to the underlying pathophysiology of GD: Unlike systemic inflammatory conditions, GD is primarily driven by specific autoantibodies, particularly TRAb. Therefore, non-specific inflammatory markers derived from peripheral blood counts may not adequately reflect the underlying autoimmune mechanisms that determine disease course.

A notable finding in our study was the high prevalence of PTC among surgically treated patients (60%), which substantially exceeds the 1–5% rate typically reported in the general GD population.^[21] This higher rate is most likely explained by the referral center bias inherent to our tertiary setting: we tend to receive patients with more complex disease, including those with coexisting thyroid nodules or suspicious ultrasonographic findings that prompted surgical referral. Importantly, all carcinomas were micropapillary (≤ 1 cm), discovered as incidental findings on pathological examination, with no preoperative nodules identified on ultrasonography, and all surgical referrals were based on ATD treatment failure rather than malignancy suspicion. Importantly, carcinoma can occur in GD patients without nodules, and the absence of nodules

on ultrasonographic examination does not exclude the risk of malignancy.^[21,22] The high rate of PTC in our surgical subgroup underscores the importance of careful ultrasonographic evaluation even in the context of GD, particularly in referral centers. This finding should be interpreted cautiously given the small number of surgically treated patients ($n=10$) in our cohort. A sensitivity analysis excluding surgically treated patients confirmed that the primary findings were not influenced by this subgroup (Suppl Table 1).

Our findings support the established prognostic relevance of TRAb in GD. Baseline and longitudinal TRAb measurements may contribute to individualized assessment of disease course alongside other clinical factors. Patients with high baseline TRAb levels may benefit from extended ATD courses (beyond 18 months) or earlier counseling regarding definitive therapy options. Current guidelines already incorporate TRAb as a factor guiding treatment duration; our data support its systematic use as a prognostic biomarker at the point of diagnosis. In clinical practice, patients with persistently elevated or rising TRAb during treatment should be closely monitored for treatment failure, and shared decision-making regarding definitive therapy should be initiated earlier in this subgroup. Conversely, early TRAb negativization during ATD therapy may serve as a positive prognostic indicator, supporting a trial of treatment discontinuation after the minimum recommended duration. However, the present findings do not establish a specific TRAb threshold for selecting treatment strategies, and treatment decisions should continue to be based on the overall clinical context and shared decision-making.

A notable strength of this work lies in its simultaneous assessment of multiple systemic inflammatory markers in relation to remission in GD, which has been rarely explored. Furthermore, the use of multivariate analysis allowed us to identify independent predictors, strengthening the validity of our findings.

Limitations

Nevertheless, certain limitations need to be considered. The retrospective design carries a risk of selection bias. The relatively small cohort and single-center setting may restrict the applicability of the findings. Indices were measured at only 1 time point, which may not adequately represent their fluctuations throughout the disease course. Several established predictors of remission were not evaluated in the present study, including thyroid volume on ultrasonography, presence and severity of Graves' orbitopathy, smoking status, family history of thyroid disease, and detailed ATD dose data throughout the treatment course. The absence of these variables represents a significant limitation and may have influenced the predictive models. A formal sample size

calculation was not performed before data collection; the final cohort of 78 patients may limit statistical power for detecting modest effect sizes. In addition, the small sample size and limited number of outcome events resulted in low precision for some regression estimates, as reflected by the very wide CIs observed for certain inflammatory indices, particularly MLR. Therefore, these effect estimates should be interpreted cautiously. The possibility that some patients currently classified as remission may relapse with extended follow-up cannot be excluded. Finally, referral center bias may affect the generalizability of our findings, particularly with respect to the high PTC rate in the surgical subgroup. Prospective multicenter studies with larger sample sizes incorporating these variables are warranted.

CONCLUSION

Baseline TRAb showed a consistent association with remission status and greater discriminatory ability than the hematological inflammatory indices examined in this cohort. In contrast, NLR, MLR, PLR, SII, SIRI, and AISI were not significantly associated with remission. Given the limited sample size and single-center design, these findings, including the exploratory TRAb cut-off, require confirmation in larger independent cohorts.

Disclosures

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital Ethics Committee (No: 184, Date: 26/09/2023).

Informed Consent: Due to the retrospective nature of the study, informed consent was waived by the ethics committee.

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Supplementary Table 1. Sensitivity analysis – excluding surgical patients (n=68)

Model	Index	TRAb OR* (95% CI)	TRAb p-value	Index OR (95% CI)/p
1	NLR	1.261 (1.134–1.402)	<0.001	1.835 (0.502–6.707)/p=0.358
2	MLR	1.260 (1.133–1.402)	<0.001	0.463 (0.000–9364)/p=0.879
3	PLR	1.260 (1.133–1.401)	<0.001	1.000 (0.982–1.019)/p=0.974
4	SII	1.260 (1.133–1.400)	<0.001	1.001 (0.997–1.005)/p=0.683
5	SIRI	1.258 (1.132–1.398)	<0.001	1.237 (0.205–7.473)/p=0.817
6	AISI	1.260 (1.133–1.401)	<0.001	1.000 (0.995–1.005)/p=0.953

Sensitivity analysis excluding the 10 surgically treated patients. Remission n=35, non-remission n=33. All TRAb p<0.001. OR: Odds ratio; CI: Confidence interval; NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; AISI: Aggregate index of systemic inflammation

Temporal Variations in Mechanical Thrombectomy for Acute Ischemic Stroke: A 1-Year Single-Center Study

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ABSTRACT

Objective: Mechanical thrombectomy (MT) improves clinical outcome in acute ischemic stroke (AIS) patients. The effect of MT over the outcome of these patients is time sensitive. The onset nature of AIS is abrupt and unpredictable. Therefore, the temporal variation of onset of AIS requires a well-organized stroke chain infrastructure to minimize its impact on the clinical outcome. The term “weekend effect” has also been reported in the field of AIS. MT as a multi-disciplinary treatment requires optimal coordination of workflow and manpower to overcome the “weekend effect.”

Materials and Methods: We retrospectively analyzed data from our prospective stroke center registry. Clinical, radiological, time-metrics, and outcome of patients who underwent MT from January to December 2023 were analyzed. The patients included in this study were divided into a daytime, nighttime, weekend, and holiday groups. Main outcome variables included favorable outcome (modified Rankin scale scores of 0–2) 3 months post-stroke as well as procedural time metrics (door-angio). Variation between subgroups was statistically analyzed.

Results: A total of 371 patients were compatible with the inclusion criteria. The median age was 68 (± 12.9) years and the median onset National Institutes of Health Stroke Scale score 17. Detailed time-metrics analysis showed that radiology to puncture and door to puncture time were significantly lower during working hours compared to other non-working hours. No significant difference was found between working hours and nighttime, weekend, or holiday hour regarding time-metrics for both transfer and mothership patients ($p > 0.001$).

Conclusion: Overall, analysis of the present data showed short time-metrics regardless of temporal variation. These findings emphasize the role of in hospital organization. In addition, our stroke flow organization model may encourage the building of similar models.

Keywords: Mechanical thrombectomy, time-metrics, weekend effect

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INTRODUCTION

Mechanical thrombectomy (MT) has revolutionized the concept of acute ischemic stroke (AIS) treatment. Randomized controlled studies have demonstrated the benefit of MT in eligible AIS patients with large vessel occlusion (LVO).^[1-7] Comprehensive stroke center (CSC) organization and a multi-disciplinary approachment are key factors for the effectiveness of MT treatment. Therefore, the temporal variation of AIS onset requires a well-working stroke chain infrastructure independent from working hours or days.

The Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register large cohort evaluated the alternation of thrombolytic treatment delivery for AIS in coherence with the pattern of AIS onset. While time of treatment was found to be an independent predictor of outcome, the number of treatment was in accordance with the diurnal pattern of stroke onset.^[8] The term “weekend effect” referring to an increase in the mortality rate for hospitalizations occurring on weekends versus weekdays has also been reported in the field of AIS.^[9-11] MT as a multi-disciplinary treatment requires optimal coordination of workflow and manpower to overcome the “weekend effect.” The Austrian EVT Study Group large cohort analysis also found that during non-working hours intrahospital MT workflow was compromised leading to worse functional outcomes^[12] Several other studies investigating the potential existence of the weekend effect over MT for AIS caused by LVO has yielded varied results.^[13-16]

In this study, we examined the potential existence of differences in MT time-metrics for AIS between daytime versus nighttime, weekend, and holiday hours in our high-volume CSC for 1 year and reviewed the data reported so far.

MATERIALS AND METHODS

In this retrospective, single-center observational study, we analyzed patients who underwent MT from January to December 2023. The 2023-year marks the highest volume of MT in our center (single-center, 421 MT patients, and 5 neuro-interventionalist). Time-metrics, including onset of symptoms, hospital arrival, radiology, and femoral puncture time, were retrieved from the database. All patients were followed up until 3 months post-procedure. Analyses were mainly focused on in-hospital pre-MT procedure time-metrics and variations between working and non-working hours.

In our center, all the AIS patients are admitted with the “neuro-code” notification. The “neuro-code” gives priority to all the suspected AIS patients admitted in the emergency room (ER), fastens the transfer to radiology, and mobilizes the anesthesiology and neuro-interventional team despite decision for MT or not. It

is applied both during daytime and nighttime, weekend, and holidays. Our CSC organization has a MT team which consists of one neuro-interventionalist, one fellow neuro-interventionalist, three stroke nurses, and 2 stroke technicians that are on duty every day from 08:00 to 17:00. During nighttime, weekends and holidays the MT team consists of the same number of persons, among them only the neuro-interventionalist and stroke technicians are on call. For mothership patients’ admission from ER, transfer to radiology and angio suite is managed by the on-site neurologist and stroke nurses. Following the decision for MT, the on-call MT team will join the hospital. For transferred patients eligible for MT, the team shall be in the hospital before the “neuro-code” announcement.

AIS patients, 18 year or older, that underwent MT within 24 h of symptom onset were included in the analyses. Patient who underwent MT after admission in the stroke unit due to clinical progression or any other reason were excluded from the analyses.

Neurologic deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS) scale. Patients were recorded as mothership or transfer patients. Onset radiological examination was performed in three different modalities:

1. Diffusion-weighted (DW), perfusion-weighted in addition, or not to vascular magnetic resonance (MR) imaging
2. Computed tomography (CT), CT perfusion in addition, or not to vascular CT imaging
3. Direct to angio-suite with CT in addition of not to vascular imaging in the angio-suite.

The patients included in this study were divided into a daytime, nighttime, weekend, and holiday groups. The daytime group referred to MT performed from 8:00 to 17:00 on weekdays (Monday to Friday), while the nighttime group referred to MT performed on weekdays from 17:00 to 8:00 the next day. Weekend days were referred as to Saturday and Sunday and Holiday days were recorded according to National Turkish Holiday Calendar.

Collected data included patients’ demographics, risk factors, NIHSS scale on onset and 24 h after procedure, use of intravenous recombinant tissue-type plasminogen activator (iv rt-PA), and type of imaging performed on onset and onset admission (mothership or transfer, respectively). Transfer patients’ first center imaging modalities were evaluated, and a second imaging was not performed in selected patients based on the on-call doctors’ decision. Triage time-metrics data were collected as follows: (1) door-to-radiology, (2) radiology-to-femoral puncture, and (3) door-to-femoral puncture.

Outcome was evaluated both using clinical and triage time-metrics findings. Clinical outcome was measured with 24 h NIHSS scale, 90-day modified Rankin scale (mRS) and mortality at 90 days. Outcome in terms of triage time-metrics was referred as door to femoral puncture in minutes.

This study conducted in accordance with the Helsinki Declaration and approved by Istanbul Aydin University Ethical Committee (approval no: 79-2025, date: April 16, 2025).

Statistical Analysis

Statistical analyses were carried out using appropriate parametric and non-parametric tests according to the distribution of the data. Non-parametric data were expressed as median value and interquartile range, parametric data as mean and standard deviation. Differences between groups were analyzed using Student's *t*-test or Mann-Whitney U, and correlation analyzes were performed with Pearson or Spearman tests. Fisher's exact test was utilized to evaluate categorical data. $P < 0.05$ was considered statistically significant. Missing data were not included in the analyses.

IBM® SPSS® Statistics 29.0.2 (Chicago, IL/USA) was used as statistical program.

RESULTS

In our center, a total of 421 MT procedures were performed from January to December 2023. Only 371 patients were compatible with the inclusion criteria. The patients excluded were patients with MT performed within more than 24 hours or missing follow-up data. Figure 1 shows the inclusion flow diagram.

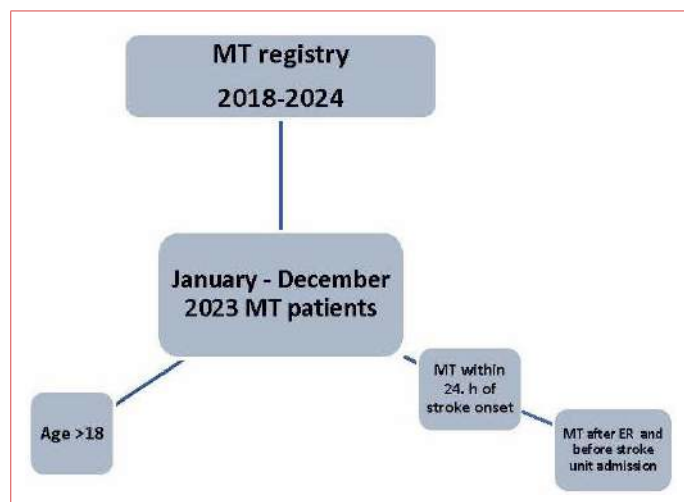


Figure 1. Patients inclusion criteria.

MT: Mechanical thrombectomy; ER: Emergency room

Overall, the median age was 68 (± 12.9) years and 189 (50.8%) of the patients were female. Among risk factors hypertension and atrial fibrillation (74.5% and 62.6%) were the highest. The median NIHSS score on admission was 17 (± 6) and 24 h NIHSS was 9 (± 7). Table 1 shows the baseline demographic features and stroke risk factors. IV tPA was administered to only 15 patients (3.7%). Due to the low IV tPA administration rate, the door to IV tPA time was not included in the outcome evaluation.

No significant difference was found between working hours and nighttime, weekend, or holiday hour in terms of demographics, risk factors, and clinical features ($p > 0.001$).

A total of 201 (54%) patients were transferred from another center and 163 (43.8%) patients were mothership patients. No significant difference was found between working hours and nighttime, weekend, or holiday hour regarding time-metrics for both transfer and mothership patients ($p > 0.001$).

The performed baseline radiological evaluation was as follows: 239 (64.2%) DW and 117 (31.5%) CT imaging protocol. A total of 29 patients were transferred directly to the angio-suite and of those 20 (69%) patients were from the transfer group and 9 (31%) patients from the mothership group. MRI imaging protocol was the most performed protocol for all working and non-working hours. The use MRI imaging protocol was significantly higher during working hours. ($p < 0.001$) Overall, MT of 150 (40.3%) patients was performed during daytime and 124 (33.3%) during nighttime.

The number of patients performed during the weekend days and holidays was 80 (21.5%) and 17 (4.6%), respectively. Door to radiology time during working hours, nighttime, weekend, and holidays were as follows: 14 ± 10.9 , 13.7 ± 9.1 , 12.5 ± 7.4 , and 10.3 ± 6.2 min. Radiology to puncture and door to puncture

Table 1. Demographic features and stroke risk factors

Demographics	
Age (mean $\pm$ SD)	68.2 $\pm$ 12.99
Female sex (n, %)	189 (50.8)
Risk factors	
Diabetes (n, %)	100 (26.9)
Hypertension (n, %)	277 (74.5)
Hyperlipidemia (n, %)	221 (59.4)
Atrial fibrillation (n, %)	233 (62.6)
CAD (n, %)	81 (21.8)
Smoking (n, %)	132 (35.5)

*CAD: Coronary artery disease, SD: Standard deviation

Table 2. Overview of patients according to admission time

	Working hours (n=150)	Night time (n=124)	Weekend (n=80)	Holiday (n=17)	p
Demographics					
Age (mean±SD)	67.9±13.7	68.5±12.3	69±11.8	65.1±16.8	0.86
Female sex (n, %)	75 (50)	62 (50)	44 (55)	7/17 (41.2)	0.73
Risk factors					
Diabetes (n, %)	39 (26)	40 (32.3)	17 (21.3)	3 (17.6)	0.25
Hypertension (n, %)	104 (69.3)	97 (78.2)	64 (80)	11 (64.7)	0.14
Hyperlipidemia (n, %)	84 (56)	84 (67.7)	44 (55)	8/17 (47.1)	0.17
Atrial fibrillation (n, %)	90 (60)	82 (66.1)	49 (61.3)	11 (64.7)	0.7
CAD (n, %)	33 (22)	32 (25.8)	12 (15)	3 (17.6)	0.3
Smoking (n, %)	55 (36.7)	47 (37.9)	24 (30)	6 (35.3)	0.67
Clinical features					
NIHSS on admission (mean±SD)	16.7±5.9	16.7±5.9	16.3±6.3	16.6±6.7	0.98
NIHSS 24 th h (mean±SD)	9.2±7.6	9.5±7.9	8.6±7.7	5.7±6.9	0.11
Time metrics					
Door to radiology (mean±SD)	14±10.9	13.7±9.1	12.5±7.4	10.3±6.2	0.51
Radiology to puncture (mean±SD)	25.9±17.9	37.3±27.7	49.6±33.4	34.8±24.1	<0.05
Door to puncture (mean±SD)	42.5±39.5	51±30	63.4±36.2	45.7±27.3	<0.05
Imaging					
CT (n, %)	54 (36)	46 (37.1)	16 (20)	1 (5.9)	0.004
MRI (n, %)	83 (55.3)	73 (58.9)	67 (83.8)	15 (88.2)	<0.05
Direct-to-angio (n, %)	18 (12)	9 (7.3)	1 (1.3)	1 (5.9)	0.036
Admission					
Transfer (n, %)	83 (55.3)	66 (53.2)	44 (55)	8 (50)	0.96
Mothership (n, %)	64 (42.7)	55 (44.4)	35 (43.8)	8 (50)	0.96

*CAD: Coronary artery disease; SD: Standard deviation; CT: Computed tomography; MRI: Magnetic resonance imaging; NIHSS: National Institutes of Health Stroke scale

time were significantly lower during working hours compared to other non-working hours. ($p<0.001$) Table 2 shows an overview of the above parameters according to the temporal variation.

In terms of clinical outcome, 24 h NIHSS did not differ between working hours and night-time, weekend and holidays. ($p>0.001$) Furthermore, 90 day mRS and mortality did not differ between working and non-working hours. (Table 3) However, door to femoral puncture was found significantly lower during working hours ($p<0.001$) (Fig. 2) Therefore, although clinical outcome was the same between working and non-working hours that the triage overall was achieved faster during working hours. In

Table 3. (a) 90 day mRS stratified by temporal variation and (b) mortality stratified by temporal variation

	mRS 0-2	mRS 3-5	mRS 6
Time			
Nighttime	68	29	26
Daytime	88	36	26
Weekend	46	20	14
Holiday	14	2	1

*mRS: Modified Rankin score

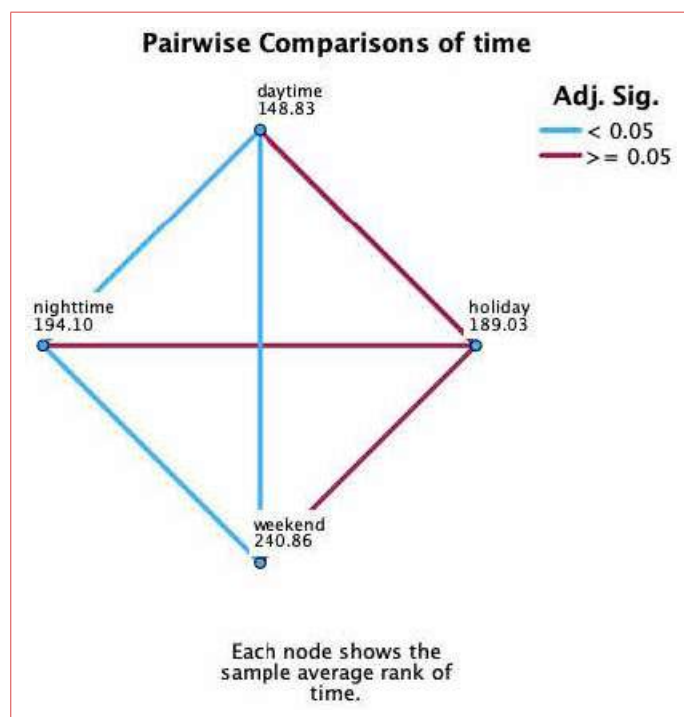


Figure 2. Door-to-femoral puncture time temporal variation.

addition, mRS 0–2 was achieved in approximately 58% of the patients and mortality overall was 23%.

DISCUSSION

This study investigates outcomes after MT in patients with AIS admitted during working hours compared with those during night-time, weekend, and holiday hours. The most prominent findings indicate that our workflow is efficient at both working hours and non-working hours in terms of door- to radiology time. However, radiology to femoral puncture and door to puncture time being shorter during working hours indicates that in hospital organization is faster in performing intervention during working hours. This could be related with the neurointerventional team not being onsite during the non-working hours.

The temporal variation of AIS onset including the “weekend effect” and the impact on clinical outcome has been analyzed since the thrombolytic treatment era and goes on recently with the introduction of MT as revascularization treatment for stroke.^[8,12-16] In this study, working hours and non-working hours median time are reported 42 and 63 min, respectively. Notably shorter than the time-metrics reported in present studies so far. We also did not find any significant relationship between working and non-working hours in terms of good outcome and mortality. Still, the good outcome rate was relatively high and mortality rate

relatively low when compared to other studies. We believe that the short time-metrics constitute an important factor in achieving this good outcome and also are a good indicator of a well-organized stroke center which should function despite the temporal variation of stroke onset. In our study, population 33% of the patients was admitted during night-time hours.

The MR CLEAN Registry of the workflow time-metrics showed a longer door-to puncture time during off-hours (including weekends) compared to on-hours (8 am–6 pm during weeks), both longer than 120 min.^[17] Other large cohorts also reported longer door-to femoral puncture times during off hours.^[12-16,18] A multi-center study also shows that the majority of MT cases occur during non-work hours and is associated with implications for hospitals implementing stroke call coverage.^[19]

Based on the past large cohort findings and time-metrics, we believe that it provides good insights about stroke center individuality in terms of organization. Our time-metrics emphasize the positive impact of good organization over time-metrics and consequently over outcome despite the effect of non-working hours.

Limitations

The main limitations of the present study are its single-center and retrospective design. Therefore, the limited comparability of our findings with those from other centers should be considered when interpreting the results.

CONCLUSION

Temporal variations of time-metrics in MT for AIS patient are an important indicator of the in-hospital stroke organization. The present findings indicating that time-metrics and outcome did not significantly differ between working and non-working hours are relevant for the careful design of stroke care, and might be applicable to other countries.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Istanbul Aydin University Ethics Committee (No: 79-2025, Date: 16/04/2025).

Informed Consent: Not declared.

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Magnetic Resonance Imaging Evaluation of Neural Injury Spectrum and Associated Secondary Musculoskeletal Sequelae in Obstetric Brachial Plexus Palsy

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ABSTRACT

Objective: The aim of this study was to characterize the spectrum of neural injury patterns and secondary musculoskeletal abnormalities on magnetic resonance imaging (MRI) in children with obstetric brachial plexus palsy (OBPP).

Materials and Methods: In this retrospective descriptive study, 56 children with OBPP who underwent brachial plexus MRI were included in the study. MRI examinations were reviewed for preganglionic and postganglionic abnormalities, distal plexus involvement, denervation-related muscle changes, and posterior humeral head subluxation. Patients were categorized as having pure preganglionic, pure postganglionic, or mixed injury patterns. Associations between muscle abnormalities, posterior humeral head subluxation, injury patterns, and patient age were evaluated using Chi-square, Fisher's exact, and Mann-Whitney U-tests, as appropriate.

Results: The median age at MRI was 10.8 months. Pure preganglionic injury was identified in 15 patients (26.8%), pure postganglionic injury in 24 (42.9%), and mixed injury in 17 (30.4%). Overall, root involvement was most frequent at C6 (83.9%), followed by C7 (75.0%) and C5 (60.7%). Neuroma-like nodular thickening was observed in 16 patients (28.6%). Muscle atrophy was present in 44 patients (78.6%), muscle edema in 13 (23.2%), and posterior humeral head subluxation in 44 patients (78.6%). An association was observed between subscapularis muscle atrophy and posterior humeral head subluxation (84.1% vs. 50.0%, $p=0.022$). Patients with muscle edema were significantly younger than those without edema ($p<0.001$).

Conclusion: OBPP demonstrates a broad spectrum of neural and musculoskeletal abnormalities on MRI. In addition to characterizing preganglionic and postganglionic injury patterns, MRI provides valuable information regarding denervation-related muscle changes and secondary shoulder deformity, enabling comprehensive assessment of disease involvement.

Keywords: Brachial plexus injuries, magnetic resonance imaging, muscle atrophy, obstetric brachial plexus palsy, shoulder subluxation

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INTRODUCTION

Obstetric brachial plexus palsy (OBPP) is one of the most common peripheral nerve injuries in newborns and results from traction injury to the brachial plexus during delivery. The severity of injury ranges from transient neuropraxia to complete root avulsion and may result in persistent motor deficits, muscle imbalance, glenohumeral deformity, and long-term functional impairment.^[1,2]

Although many infants with OBPP experience spontaneous functional recovery, a subset develop persistent neurological deficits that may require imaging evaluation and surgical consideration.^[2,3] Accurate characterization of the location and extent of neural injury is therefore essential for treatment planning and prognostic assessment. Clinical examination and electrodiagnostic studies provide important information regarding functional impairment; however, they may be limited in young infants and may not accurately localize the level of injury.^[4] Although surgical exploration remains the reference standard for defining the extent of neural injury, its invasive nature limits its use as a diagnostic tool.^[2,3] Magnetic resonance imaging (MRI) has emerged as a valuable non-invasive modality for evaluating both preganglionic and postganglionic components of the brachial plexus.^[4,5] In addition to identifying root avulsion and pseudomeningocele formation, MRI provides comprehensive assessment of postganglionic nerve abnormalities and denervation-related musculoskeletal changes.^[5,6]

Previous studies have primarily focused on the diagnostic performance of MRI for detecting preganglionic injuries, particularly root avulsion.^[2-4] However, OBPP represents a spectrum of abnormalities that may involve multiple root levels and both preganglionic and postganglionic segments of the brachial plexus.^[4,5] In addition, denervation-related muscular changes and secondary glenohumeral abnormalities may provide complementary information regarding the chronicity and severity of injury.^[7,8] Despite the growing use of MRI in OBPP, studies comprehensively evaluating neural abnormalities together with associated musculoskeletal manifestations remain limited.^[2]

The aim of this study was to characterize the MRI spectrum of neural injury patterns and secondary musculoskeletal changes in children with OBPP and to explore the relationship between neural abnormalities and associated musculoskeletal manifestations.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective descriptive study was approved by the Ankara University Faculty of Medicine Human Research Ethics

Committee (approval no: İ06-637-26 date: June 18, 2026) and was in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study. The institutional radiology database was retrospectively reviewed to identify children diagnosed with OBPP who underwent brachial plexus MRI between March 2014 and March 2026 at a tertiary referral pediatric hospital.

Inclusion criteria were a clinical diagnosis of OBPP and availability of MRI examinations with sufficient image quality for detailed assessment of neural injury patterns and secondary musculoskeletal changes. Exclusion criteria included inadequate image quality and brachial plexus injuries related to non-obstetric traumatic causes.

A total of 56 patients were included in the final study cohort.

MRI Evaluation

All MRI examinations were performed on a 1.5-T scanner (Ingenia, Philips Medical Systems, Eindhoven, The Netherlands) using a dedicated neurovascular coil. Imaging was performed with the patient in the supine position, including both shoulders, with the arms maintained in a neutral position for brachial plexus evaluation. MRI examinations were performed under institutional pediatric sedation protocols.

The MRI protocol consisted of sagittal T2-weighted turbo spin-echo (TSE), axial and coronal T1-weighted TSE (TR/TE, 600/14 ms; field of view, 16 cm; slice thickness, 2–3 mm), axial and coronal T2-weighted TSE (TR/TE, 3500/80 ms; field of view, 16 cm; slice thickness, 2–3 mm), balanced fast field echo sequences (TR/TE, 6/3 ms; field of view, 16 cm; slice thickness, 1 mm), and coronal short TI inversion recovery sequences (TR/TE, 2400/60 ms; field of view, 16 cm; slice thickness, 2–3 mm).

All MRI examinations were reviewed by a pediatric radiologist with 10 years of experience in pediatric neuroimaging. The reviewing radiologist was aware that all MRI examinations were performed for suspected OBPP, and patient age was available during image interpretation. However, the radiologist was blinded to the clinically affected side, clinical severity, physical examination findings, and other relevant clinical information.

Preganglionic abnormalities, including root avulsion and pseudomeningocele, were recorded at each root level (C5–T1). Postganglionic abnormalities were assessed at the interscalene level and included signal abnormalities, nerve thickening, and neuroma-like changes (Fig. 1). The affected root levels and involved distal brachial plexus segments (trunks, divisions, and cords) were also recorded.

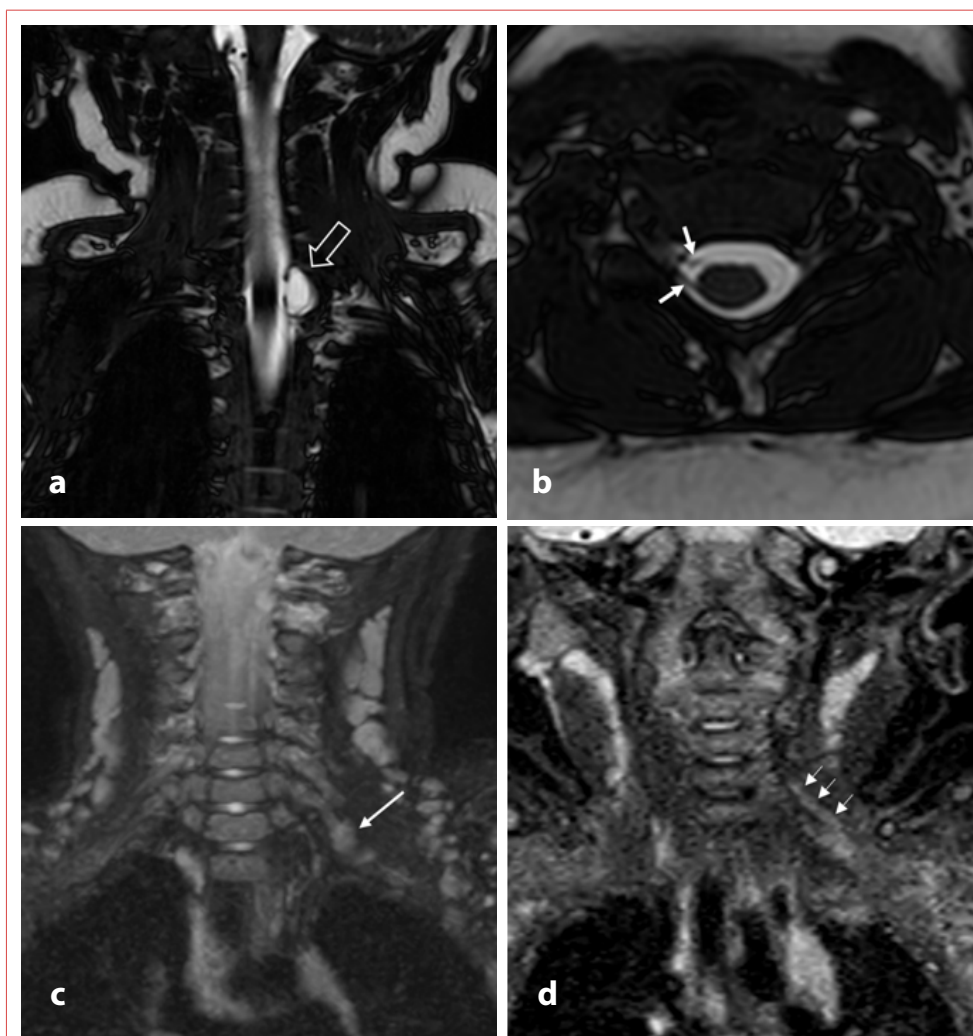


Figure 1. Representative magnetic resonance imaging findings of preganglionic and postganglionic injury in obstetric brachial plexus palsy. Coronal **(a)** and axial **(b)** heavily T2-weighted images demonstrate a left C7 pseudomeningocele (open arrow) and associated root avulsion, representing preganglionic injury. Normal dorsal and ventral nerve rootlets are shown on the contralateral side (white arrows). Coronal short TI inversion recovery (STIR) maximum intensity projection image **(c)** and coronal STIR image **(d)** demonstrate postganglionic abnormalities, including neuroma-like nodular thickening (long arrow) and asymmetric thickening with increased signal intensity of the left C5 and C6 roots at the interscalene level (short arrows).

Patients were categorized according to MRI findings as having pure preganglionic injury, pure postganglionic injury, or mixed injury (Fig. 2). Distal signal abnormalities occurring at the same level as a definite preganglionic lesion were not considered independent postganglionic injuries for classification purposes. For descriptive root-level analysis, exclusive postganglionic involvement was defined as postganglionic signal abnormality/thickening without accompanying preganglionic abnormalities at the corresponding root level.

Denervation-related muscular abnormalities were assessed in the supraspinatus, infraspinatus, subscapularis, and deltoid muscles. Muscle atrophy was graded using a semiquantitative visual scoring system: Grade 0: no atrophy, Grade 1: Mild-to-moderate atrophy, and Grade 2: Severe atrophy with marked volume loss, with or without fatty infiltration. The presence of muscle edema was recorded as a binary variable (present/absent), based on increased T2-weighted signal intensity within the affected muscle.

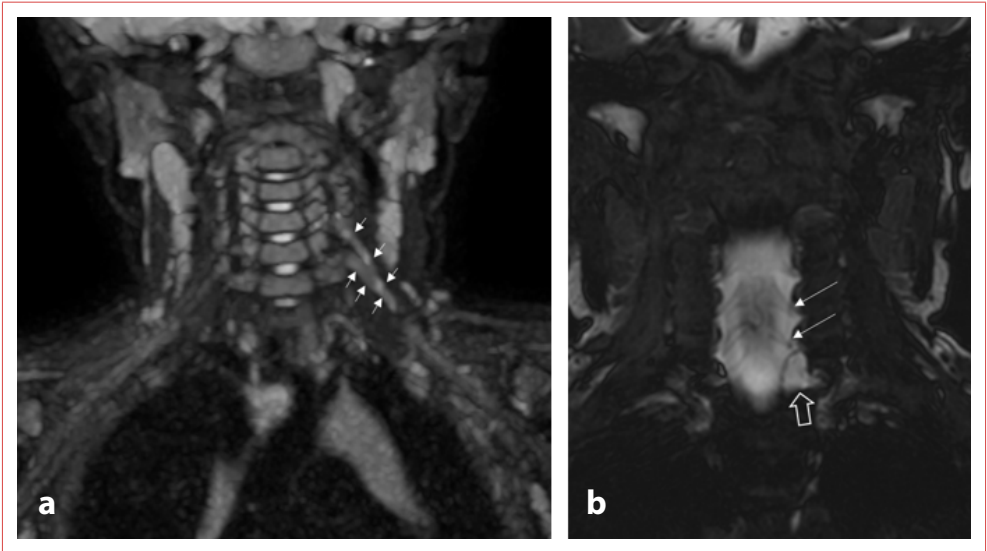


Figure 2. Mixed injury pattern in obstetric brachial plexus palsy. Coronal short TI inversion recovery maximum intensity projection image **(a)** demonstrates asymmetric thickening and increased signal intensity of the left C5 and C6 roots at the interscalene level, consistent with postganglionic injury (small arrows). In the same patient, coronal heavily T2-weighted image **(b)** demonstrates intact left C5 and C6 roots (long arrow), whereas a left C7 root avulsion and associated pseudomeningocele (open arrow) are present, consistent with preganglionic injury.

Posterior humeral head subluxation was evaluated and recorded as present or absent.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 23 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (interquartile range [IQR]), whereas categorical variables were presented as frequencies and percentages. Comparisons between categorical variables were performed using the Chi-square test or Fisher’s exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U-test. A two-sided $p<0.05$ was considered statistically significant.

To assess interobserver agreement, a randomly selected subset of 20 MRI examinations was independently reviewed by a second pediatric radiologist with 8 years of experience, blinded to the first reader’s interpretations. Cohen’s kappa was calculated for binary variables, and weighted Cohen’s kappa was used for semiquantitative muscle atrophy grading.

RESULTS

A total of 56 children with OBPP were included in the study. The median age at MRI was 10.8 months (IQR, 5.4–17.0 months; range, 1.5–38.0 months). The cohort included 28 girls (50.0%) and 28 boys (50.0%); left-sided involvement was observed in

33 patients (58.9%). Demographic characteristics and overall MRI findings are summarized in Table 1.

Table 1. Demographic characteristics and overall MRI findings	
Variable	Value (%)
Number of patients	56
Age at MRI, months, median (IQR; range)	10.8 (5.4–17.0; 1.5–38.0)
Female sex	28 (50.0)
Male sex	28 (50.0)
Right-sided involvement	23 (41.1)
Left-sided involvement	33 (58.9)
Pure preganglionic injury	15 (26.8)
Pure postganglionic injury	24 (42.9)
Mixed injury	17 (30.4)
Pseudomeningocele	31 (55.4)
Root avulsion	32 (57.1)
Neuroma-like thickening	16 (28.6)
Muscle edema	13 (23.2)
Any muscle atrophy	44 (78.6)
Posterior humeral head subluxation	44 (78.6)
MRI: Magnetic Resonance Imaging, IQR: Interquartile range	

Table 2. Distribution of root-level MRI abnormalities

Root level	Overall involvement ^a n (%)	Pseudomeningocele n (%)	Root avulsion n (%)	Postganglionic abnormality n (%)	Exclusive postganglionic involvement ^b n (%)
C5	34 (60.7)	8 (14.3)	11 (19.6)	31 (55.4)	23 (41.1)
C6	47 (83.9)	15 (26.8)	17 (30.4)	41 (73.2)	29 (51.8)
C7	42 (75.0)	20 (35.7)	21 (37.5)	39 (69.6)	20 (35.7)
C8	20 (35.7)	6 (10.7)	6 (10.7)	17 (30.4)	13 (23.2)
T1	3 (5.4)	1 (1.8)	1 (1.8)	3 (5.4)	2 (3.6)

MRI: Magnetic resonance imaging. ^aOverall involvement was defined as the presence of any abnormality at the corresponding root level, including pseudomeningocele, root avulsion, or postganglionic signal abnormality/thickening. ^bExclusive postganglionic involvement indicates postganglionic abnormality without a concomitant preganglionic lesion at the same root level

Based on MRI findings, pure preganglionic injury was identified in 15 patients (26.8%), pure postganglionic injury in 24 patients (42.9%), and mixed injury in 17 patients (30.4%).

Neural abnormalities involved both preganglionic and postganglionic portions of the brachial plexus. Overall root-level involvement was most frequently observed at C6 (83.9%), followed by C7 (75.0%) and C5 (60.7%). Exclusive postganglionic involvement was also most common at C6 (51.8%), followed by C5 (41.1%) and C7 (35.7%). Detailed root-level distributions of pseudomeningocele, root avulsion, postganglionic abnormalities, and exclusive postganglionic involvement are presented in Table 2.

Additional distal plexus involvement was most frequently observed at the trunk level (41.1%), followed by the division level (17.9%) and the cord level (1.8%). Neuroma-like nodular thickening was identified in 16 patients (28.6%).

Muscle atrophy was present in 44 patients (78.6%), whereas muscle edema was observed in 13 patients (23.2%). Severe atrophy (grade 2) affecting at least one muscle was identified in 4 patients (7.1%). The subscapularis and infraspinatus muscles were the most frequently affected muscles, and posterior humeral head subluxation was present in 44 patients (78.6%). No significant association was observed between injury pattern classification and the presence of muscle atrophy (Fig. 3).

The association between individual muscle atrophy and posterior humeral head subluxation is summarized in Table 3. Subscapularis muscle atrophy was significantly associated with posterior humeral head subluxation (84.1% vs. 50.0%, $p=0.022$), whereas infraspinatus atrophy demonstrated a similar trend that did not reach statistical significance (77.3% vs. 50.0%, $p=0.081$). No significant associations were observed for supraspinatus or deltoid atrophy.

Median age was significantly lower in patients with muscle edema compared to those without muscle edema (4.0 months [IQR, 2.8–6.0] versus 12.0 months [IQR, 9.1–20.0]; $p<0.001$).

Interobserver agreement was excellent for root avulsion ($\kappa=1.00$), pseudomeningocele ($\kappa=0.90$), neuroma-like thickening ($\kappa=0.88$), and muscle edema ($\kappa=0.83$). For semiquantitative muscle atrophy grading, weighted Cohen's kappa values were 0.78 for the supraspinatus, 0.78 for the infraspinatus, 0.83 for the subscapularis, and 1.00 for the deltoid muscle. Posterior humeral head subluxation demonstrated substantial agreement ($\kappa=0.63$). Overall, these findings indicate substantial to excellent interobserver agreement across all evaluated imaging parameters.

DISCUSSION

In this retrospective MRI-based study of children with OBPP, we comprehensively evaluated both neural injury patterns

Table 3. Association between individual muscle atrophy and posterior humeral head subluxation

Muscle atrophy	No subluxation (n=12)	Posterior Subluxation (n=44)	p
Supraspinatus atrophy, n (%)	4 (33.3)	16 (36.4)	1.000
Infraspinatus atrophy, n (%)	6 (50.0)	34 (77.3)	0.081
Subscapularis atrophy, n (%)	6 (50.0)	37 (84.1)	0.022*
Deltoid atrophy, n (%)	6 (50.0)	27 (61.4)	0.522

p-values calculated using Fisher's exact test. * $p<0.05$.



Figure 3. Secondary musculoskeletal abnormalities in obstetric brachial palsy. Coronal T1-weighted image (a) demonstrates severe fatty atrophy of the left subscapularis muscle (short white arrows). The contralateral normal shoulder is shown in (b). Axial T1-weighted image (c) demonstrates marked atrophy of the subscapularis (short white arrows), infraspinatus (black arrows), and deltoid muscle (asterisk). The contralateral normal shoulder is shown in (d). Axial T2-weighted image (e), obtained in the same patient, demonstrates posterior humeral head subluxation (open arrow) and associated glenoid dysplasia (long arrow).

and secondary musculoskeletal abnormalities. The principal findings were as follows: (1) C6 was the most frequently involved root level, followed by C7 and C5; (2) both preganglionic and

postganglionic abnormalities were common, with mixed injury patterns observed in nearly one-third of patients; (3) denervation-related muscular abnormalities and posterior

humeral head subluxation were highly prevalent; (4) an association was observed between subscapularis muscle atrophy and posterior humeral head subluxation; and (5) muscle edema was predominantly observed in younger patients. Collectively, these findings underscore the broad spectrum of neural and musculoskeletal manifestations that can be identified on MRI in children with OBPP.

The distribution of root-level abnormalities in our cohort was generally consistent with the known predominance of upper plexus involvement in OBPP.^[9-12] C6 was the most frequently involved root level, followed by C7 and C5. Although C7 abnormalities were common, isolated C7 involvement was rare, and most cases occurred in combination with C5 and/or C6 abnormalities, reflecting extended upper plexus involvement rather than isolated middle-root injury. This pattern may partly reflect referral bias, as children referred for MRI often have persistent deficits or more extensive injuries, whereas milder C5–C6 lesions may recover spontaneously and remain underrepresented in imaging-based cohorts.^[2,4]

MRI demonstrated abnormalities involving both preganglionic and postganglionic portions of the brachial plexus. Pure postganglionic injury was the most common pattern; however, mixed injury was identified in approximately one-third of patients. These findings emphasize the heterogeneous nature of OBPP and highlight that preganglionic and postganglionic abnormalities frequently coexist. Although preganglionic injuries, particularly root avulsions, have traditionally received greater attention due to their prognostic significance and implications for surgical planning,^[3,4,13] our findings demonstrate that postganglionic abnormalities are also common in children undergoing MRI evaluation for OBPP. Moreover, substantial rates of muscle atrophy and posterior shoulder subluxation were observed across all injury patterns. These observations suggest that clinically relevant secondary musculoskeletal changes are not limited to preganglionic injuries and may also develop in patients with postganglionic or mixed lesions. Therefore, comprehensive MRI assessment should extend beyond the detection of root avulsion and include evaluation of distal neural abnormalities and their musculoskeletal consequences.

Secondary musculoskeletal abnormalities were highly prevalent in our cohort. Overall, muscle atrophy and posterior shoulder subluxation were each observed in 78.6% of patients. Among the evaluated muscles, subscapularis and infraspinatus were the most frequently affected. The predominance of subscapularis and infraspinatus involvement is consistent with previous reports describing substantial denervation-related changes in the shoulder girdle muscles of children with OBPP.^[7,8,14] The higher frequency of posterior

shoulder subluxation among patients with subscapularis atrophy in our cohort is consistent with the proposed role of denervation-related muscle imbalance in the development of glenohumeral deformity in OBPP.^[7,8] However, because this was an exploratory analysis involving multiple comparisons, this finding should be interpreted with caution. Previous studies have shown that glenohumeral instability and posterior humeral head subluxation may develop during early infancy and progressively evolve into secondary glenohumeral deformity, underscoring the importance of recognizing shoulder involvement in children with persistent OBPP.^[15,16]

The frequency of muscle atrophy did not differ significantly across injury patterns, whereas muscle edema was significantly more common in younger patients. Together, these findings suggest that denervation-related muscle changes may not be determined solely by the anatomical pattern of neural injury. Factors such as injury severity, duration of denervation, and timing of imaging may also contribute to the extent of muscular involvement observed on MRI. Given the recognized progression from denervation edema to chronic muscle atrophy, the pattern of muscular abnormalities may vary according to the stage of denervation at the time of imaging.^[17,18]

Limitations

The present study has several limitations. First, its retrospective design may have introduced selection bias. Second, surgical findings, electrodiagnostic studies, and long-term clinical outcomes were not consistently available for correlation with MRI findings. Therefore, the diagnostic accuracy of individual MRI findings could not be systematically assessed. Third, muscle atrophy was evaluated using a semiquantitative visual grading system rather than quantitative volumetric measurements. The analyses evaluating the association between individual muscle atrophy and posterior humeral head subluxation were exploratory. As multiple comparisons were performed without formal adjustment, these findings should be interpreted with caution and require confirmation in larger studies. Finally, this was a single-center study, which may limit the generalizability of our findings. Although the study covered a 12-year period, all MRI examinations were performed on the same MRI scanner using a standardized institutional imaging protocol, reducing potential variability in image acquisition. Nevertheless, this study provides a comprehensive overview of both neural and musculoskeletal MRI findings in children with OBPP.

CONCLUSION

MRI demonstrates a broad spectrum of neural and musculoskeletal abnormalities in children with OBPP. In addition to characterizing preganglionic and postganglionic injury patterns, MRI provides valuable information regarding secondary

musculoskeletal changes, including muscle denervation and glenohumeral deformity. These findings highlight the value of MRI in the comprehensive evaluation of OBPP, extending beyond the detection of root avulsion to include associated distal neural and musculoskeletal abnormalities.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (No: İ06-637-26, Date: 18/06/2026).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

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Which Ankle Morphological Features are Associated with Anterior Talofibular Ligament Injury? An Ordinal Regression Analysis

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ABSTRACT

Objective: The objective of the study was to determine whether distal tibiofibular and talar morphological features are associated with the severity of anterior talofibular ligament (ATFL) injury after acute lateral ankle sprain.

Materials and Methods: This retrospective observational study included 280 adults who underwent magnetic resonance imaging (MRI) for acute lateral ankle sprain between January 2018 and December 2024. ATFL injury was classified according to the four-level Schneck system (grade 0–III); using a grade-stratified design, 70 patients were selected at random within each grade. Eighteen radiographic and MRI-based morphological parameters were assessed by blinded observers. Between-grade comparisons used univariate tests with false discovery rate correction. Independent associations with increasing ATFL injury grade were evaluated using ordinal logistic regression.

Results: Nine of 18 morphological parameters differed significantly across injury grades after false discovery rate correction. In the multivariable ordinal model, a smaller talar radius (odds ratio [OR]=0.761/mm, 95% confidence interval [CI]: 0.696–0.832), greater talar height (OR=1.095/mm, 95% CI: 1.047–1.145), higher distal tibial lateral angle (OR=1.112/degree, 95% CI: 1.036–1.195), longer anterior tubercle (OR=1.183/mm, 95% CI: 1.055–1.327), and greater talar dome–distal fibula distance (OR=1.428/mm, 95% CI: 1.124–1.811) were independently associated with higher injury grades. I-type fibular notch morphology was associated with lower odds of a higher grade than C-type morphology (OR=0.295, 95% CI: 0.154–0.564). The model had a Nagelkerke pseudo- R^2 of 0.286.

Conclusion: Talocrural osseous morphology is independently associated with acute ATFL injury severity. These routinely measurable features may contribute to anatomy-informed risk assessment, but the findings are cross-sectional and hypothesis-generating and should not be interpreted as individual-level predictors.

Keywords: Anatomic variation, ankle injuries, anterior talofibular ligament, magnetic resonance imaging, morphometry

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INTRODUCTION

Ankle sprains are among the most common musculoskeletal injuries in both athletes and the general population, accounting for approximately 5–20% of all sports-related injuries.^[1,2] Most of these injuries involve lateral ankle sprains, typically resulting from a plantarflexion–inversion mechanism. The anterior talofibular ligament (ATFL), the weakest component of the lateral ligament complex, is the most frequently injured ligament and may be affected either in isolation or together with the calcaneofibular ligament (CFL).^[3] ATFL injuries often present with acute pain, swelling, and functional impairment; if inadequately treated, they can progress to chronic ankle instability (CAI), recurrent sprains, proprioceptive deficits, and, ultimately, post-traumatic osteoarthritis.^[4] Previous studies indicate that approximately 20–40% of patients with CAI continue to experience persistent instability and functional limitations despite appropriate rehabilitation.^[5]

Recent studies have suggested that, in addition to ligamentous integrity, joint morphology may also play a decisive role in the predisposition to lateral instability. Variations in the distal tibiofibular joint (DTFJ) – such as a shallow or wide tibial incisura, decreased fibular overlap, or an anteriorly positioned fibula – may negatively affect ankle stability.^[6–11] Likewise, talar morphology influences the orientation of the articular contact surfaces and load distribution. Asymmetry between the medial and lateral radii of curvature of the talar dome has been proposed to modulate rotatory stabilization and ligament loading,^[12] alterations in the orientation of the talar articular facets have been reported in CAI without demonstrable differences in talar curvature,^[13] and the osseous configuration of the subtalar joint has also been implicated.^[14] These morphological factors may alter the stretching and rupture mechanisms of the ATFL and, when combined with additional risk factors such as high body mass index (BMI) or repetitive microtrauma, may increase the likelihood of injury. However, studies investigating these associations remain limited and report conflicting results; while some researchers have identified significant relationships between distal tibial incisura depth and chronic instability, others have not confirmed this link.^[7,9–11,15] Moreover, most previous studies have relied on single-parameter assessments using MRI or radiography alone, and the direct relationships between morphological characteristics, comorbid factors, and ATFL injury severity have not been adequately explored. Consequently, determining whether ligament injury severity is influenced not only by traumatic mechanisms but also by individual anatomical variations remains an important gap in the current literature, and therefore this study was designed to address this uncertainty.

This study aims to investigate the relationship between distal tibiofibular and talar morphology and MRI-determined ATFL injury status. The research question asks whether specific osseous morphological characteristics differ across the four Schneck grades of ATFL injury, from an intact ligament to complete rupture, and whether any such characteristics are independently associated with injury severity after adjustment for other anatomical and demographic factors. The working hypothesis is that morphological variations of the DTFJ and the talar dome are associated with ATFL injury, without a prespecified direction of effect for individual parameters.

MATERIALS AND METHODS

This retrospective observational imaging study was conducted at a single tertiary orthopedic center between January 2018 and December 2024. The study protocol was approved by the Institutional Review Board of the Clinical Research Ethics Committee of University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital (IRB no: 5097, date: September 30, 2025) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All imaging data were anonymized before analysis, and no additional interventions were undertaken for research purposes. All magnetic resonance imaging (MRI) and radiographic examinations were retrieved from the institutional Picture Archiving and Communication System (PACS). MRI scans were obtained using a 1.5-T system with standard ankle protocols, including axial, coronal, and sagittal proton density–fat suppressed (PD-FS) or T2-weighted sequences (slice thickness: 3 mm, matrix: 256×256). Standardized radiographs – anteroposterior mortise views of the ankle at 15–20° internal rotation, lateral ankle views, and dorsoplantar foot views – were acquired within ±4 weeks of MRI evaluation. All radiographs were obtained under weight-bearing conditions in accordance with the standard institutional protocol.

Patients who underwent MRI for acute lateral ankle sprain within the study period were retrospectively reviewed. Individuals aged 18 years or older were eligible. Acute lateral ankle sprain was defined based on a compatible trauma mechanism (inversion/plantarflexion injury), acute onset of lateral ankle pain and swelling within 7 days of trauma, and physical examination findings including localized tenderness over the ATFL and/or CFL, and positive anterior drawer or talar tilt tests. MRI confirmation required imaging findings consistent with an acute lateral ankle sprain, including soft-tissue edema, joint effusion, or signal alteration of the lateral ligament complex. Patients in whom the ATFL was intact on MRI despite a clinically confirmed acute sprain were classified as Schneck grade 0. Inclusion criteria were: (1) Evaluable MRI

findings regarding the integrity or rupture of the ATFL, and (2) availability of a complete standardized radiographic series, including weight-bearing mortise and lateral ankle radiographs and a weight-bearing dorsoplantar foot radiograph, obtained within ± 4 weeks of MRI. Height and weight recorded in the hospital information system at the time of the index admission were used to calculate BMI. Exclusion criteria included prior ankle surgery or fracture, high-grade syndesmotic injury or deltoid ligament rupture, osteochondral lesions larger than 10 mm, advanced degenerative or inflammatory arthropathies, and poor-quality or non-standard images. Osteochondral lesions larger than 10 mm were excluded because associated subchondral collapse or contour irregularity of the talar dome would compromise the reliability of the talar radius, talar height, and tibiotalar sector angle measurements. Patients meeting all criteria were included in the final analysis (Fig. 1).

The primary dependent variable was the degree of ATFL injury graded on MRI according to the Schneck et al. classification system: Grade 0, intact ligament; Grade I, preserved continuity with increased signal intensity or stretching; Grade II, partial tear; and Grade III, complete rupture or non-visualization of the ligament.^[16] All four grades were analysed as a four-level ordinal outcome variable without collapsing categories. ATFL grading was performed by two orthopedic surgeons who independently reviewed all MRI examinations and assigned the final grade by consensus. These two observers were not involved in the morphological measurements and were blinded to all radiographic parameters, to the clinical findings, and to the measurements performed by the other observer pair.

Sample Size

An a priori power analysis was performed before data collection. As the primary analysis was planned as an ordinal logistic regression with ATFL injury grade as a four-level ordinal outcome, sample size was estimated using the method described by Whitehead for ordered categorical data.^[17] Assuming a balanced distribution across the four Schneck grades, a two-sided alpha of 0.05, and 80% power, a total of 279 patients (approximately 70/grade) was required to detect an odds ratio (OR) of 1.35 or greater per one standard deviation increase in a continuous predictor. A target of 70 patients per Schneck grade was therefore set. Sampling was grade-stratified rather than consecutive: all patients undergoing MRI for acute lateral ankle sprain within the study period were screened, assessed for eligibility, and assigned to their Schneck grade. Within each grade, 70 patients were then selected at random from all eligible patients of that grade using the random case selection function of Statistical Package for the Social Sciences (SPSS), and screening for that grade was stopped once the target was reached. This balanced design was adopted for analytical purposes, to maximize statistical efficiency of the ordinal regression model across all four grades; the resulting 25% distribution per grade is therefore a feature of the sampling frame and does not reflect the population prevalence of ATFL injury grades. Of 400 patients identified, 362 were assessed for eligibility, and 280 were included (Fig. 1).

All morphological assessments were performed digitally on PACS using millimetric calibration by two other orthopedic surgeons with at least 10 years of experience in musculoskeletal trauma and sports surgery, who were not involved in ATFL

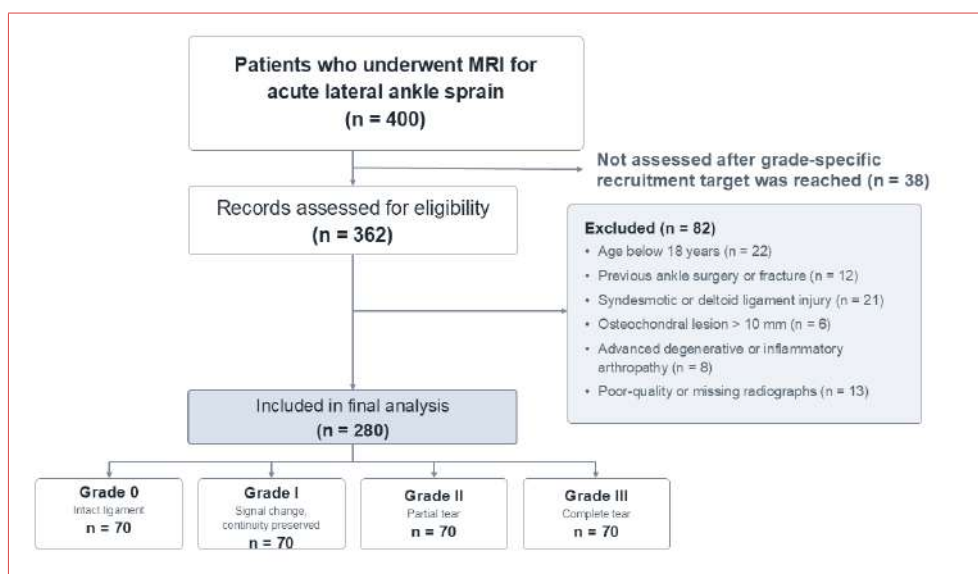


Figure 1. Study flow diagram.

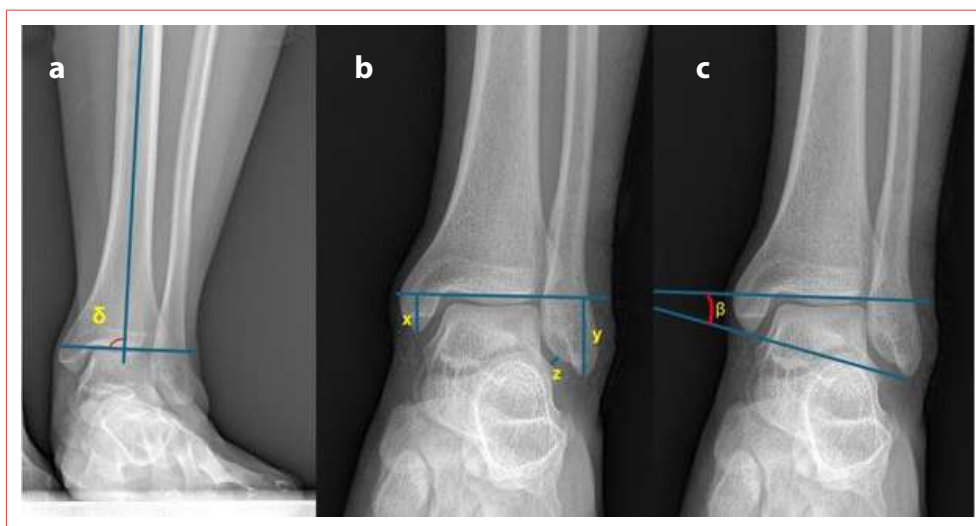


Figure 2. Radiographic measurements on the mortise ankle radiograph. **(a)** Measurement of the distal tibial lateral angle (DTLA), with δ representing the angle between the longitudinal axis of the distal tibial shaft and the tibial plafond line. **(b)** Measurement of medial malleolar length (x, MML), lateral malleolar length (y, LML), and talar dome–distal fibula distance (z, TD-FD). The lateral-to-medial malleolar length ratio (LMMLR) was calculated as y/x . **(c)** Measurement of the talocrural angle (TCA), with β representing the angle between the tibial plafond line and the line connecting the tips of the medial and lateral malleoli.

grading. These observers were blinded to clinical data, to the assigned ATFL injury grade, and to each other's measurements. Radiographic and MRI-based morphological parameters were evaluated.

Morphological Measurements

On radiographs, the distal tibial lateral angle (DTLA, $^{\circ}$) was measured on the mortise view as the angle between the longitudinal axis of the distal tibial shaft and the line connecting the most distal articular margins of the tibial plafond (Fig. 2a). Lateral malleolar length (LML) and medial malleolar length (MML) were measured perpendicularly from the tibial plafond line to the distal malleolar tips, and their ratio (lateral-to-MML ratio) was calculated. The talar dome–distal fibula distance (TD-FD) represented the shortest horizontal distance between the lateral border of the talar dome and the inner cortex of the distal fibula (Fig. 2b). The talocrural angle (TCA, $^{\circ}$) was measured on the mortise radiograph as the angle between a line along the tibial plafond articular surface and a line connecting the tips of the medial and lateral malleoli, with a reported normal range of 8° – 15° using this reference method (Fig. 2c).^[18]

The talar convexity angle (TCOA, $^{\circ}$) was measured on the lateral radiograph according to the method described by Vuurberg et al. Three points were identified: the posterior tubercle of

the talus (P1), the most proximal point of the talar dome (P2), and the deepest point of the transition between the talar body and the talar neck (P3). The angle formed between the lines P1–P2 and P2–P3 was recorded as the TCoA (Fig. 3a).^[19] A best-fit circle was fitted to the entire articular contour of the talar dome on the lateral radiograph, extending from the anterior to the posterior articular margin, and the talar radius (r, mm) was recorded as the radius of this circle. The tibiotalar sector angle (α , $^{\circ}$) was measured as the angle subtended at the center of this circle by two lines directed towards the anterior and posterior margins of the tibial plafond, representing the proportion of the talar dome covered by the tibial plafond. Talar height (h, mm) was measured on the lateral radiograph as the perpendicular distance from the highest point of the talar dome to the inferior talar cortex (Fig. 3b). The fibulotalar angle (FTA, $^{\circ}$) was measured on the lateral radiograph as the angle between the longitudinal axis of the fibula and a tangent to the talar dome (Fig. 3c).

Fibular position (FP, %) was calculated on the lateral radiograph as the ratio of posterior displacement of the distal fibula to the total anterior–posterior tibial depth, multiplied by 100 (Fig. 4a). The talocalcaneal angle (TCaLA, $^{\circ}$) on dorsoplantar foot radiographs was defined as the angle between the longitudinal axes of the talus and calcaneus (Fig. 4b).

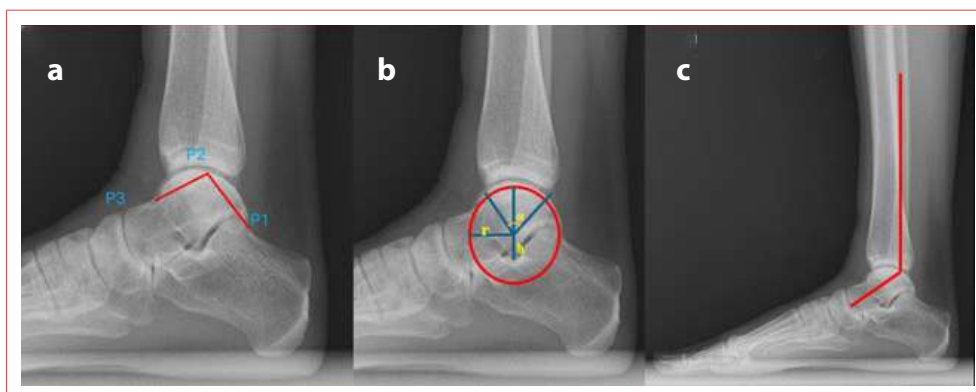


Figure 3. Radiographic measurements of talar morphology on the lateral ankle radiograph. **(a)** Measurement of the talar convexity angle (TCoA). P1 indicates the posterior tubercle of the talus, P2 the most proximal point of the talar dome, and P3 the deepest point of the transition between the talar body and talar neck; the angle P1–P2–P3 represents the TCoA. **(b)** Measurement of the talar radius (r), tibiotalar sector angle (α), and talar height (h) using a best-fit circle of the talar dome. **(c)** Measurement of the fibulotalar angle, defined by the longitudinal axis of the fibula and a tangent to the talar dome.

Fibular notch depth (FND, mm) was measured as the perpendicular distance between the line connecting the tips of the anterior and posterior tibial tubercles and the deepest point of the notch, 10 mm proximal to the tibial plafond,

and was analysed as a continuous variable rather than as a classification criterion. The anterior tubercle length (AFL, mm) and posterior tubercle length (PFL, mm) of the fibular notch were measured on axial MRI as described by Misir et al.,^[20]

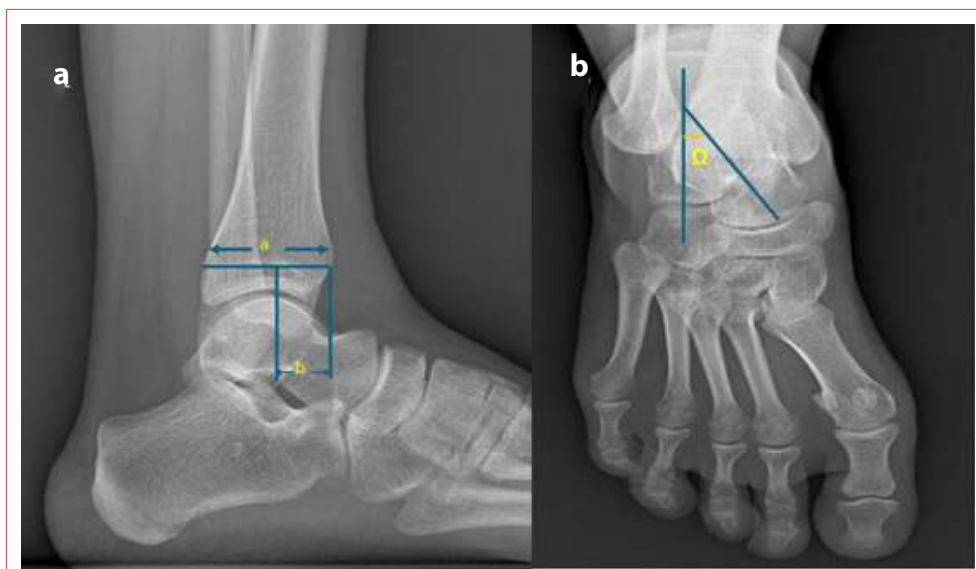


Figure 4. Additional radiographic measurements of ankle and hindfoot morphology. **(a)** Measurement of fibular position (FP). a represents the total anterior–posterior tibial depth and b represents the posterior displacement of the distal fibula; FP was calculated as $(b/a) \times 100$. **(b)** Measurement of the talocalcaneal angle (TCaA) on the dorsoplantar foot radiograph, with Ω representing the angle between the longitudinal axes of the talus and calcaneus.

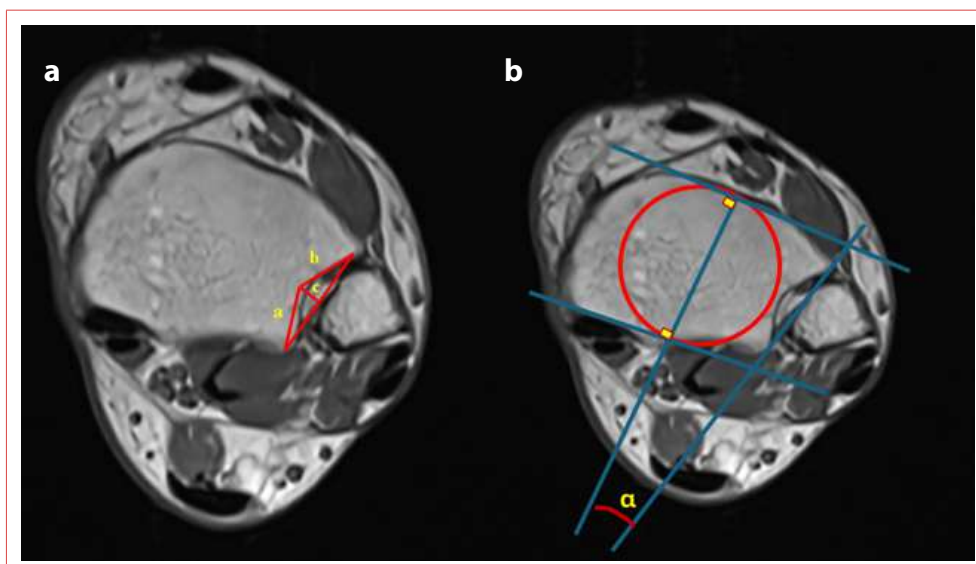


Figure 5. Magnetic resonance imaging-based measurements of fibular notch morphology. **(a)** Measurement of the anterior and posterior tubercle lengths and the anterior-posterior tubercle angle (APFA). a=Represents the posterior tubercle length, b=The anterior tubercle length, and c=The APFA. **(b)** Measurement of fibular notch version, with α=Representing the version angle.

and the angle formed between the anterior and posterior tubercle lines was recorded as the anterior-posterior tubercle angle (APFA, °) (Fig. 5a). The fibular notch version (FNV, °) was measured as the angle between the anterior-posterior axis of the fibular notch and the a line perpendicular to the posterior cortical line of the distal tibia on axial MRI (Fig. 5b).

Fibular notch morphology was classified visually on axial MRI according to the three-type system described by Taser et al.^[21]

and subsequently applied by Mısır et al.^[20] as C-type (concave), I-type (shallow and flat), or r-type (rounded, with a smooth transition between the tubercles) (Fig. 6).

Measurement Reliability

All continuous morphological parameters were measured independently by two observers, and the mean of the two measurements was used for the primary analyses. For reliability

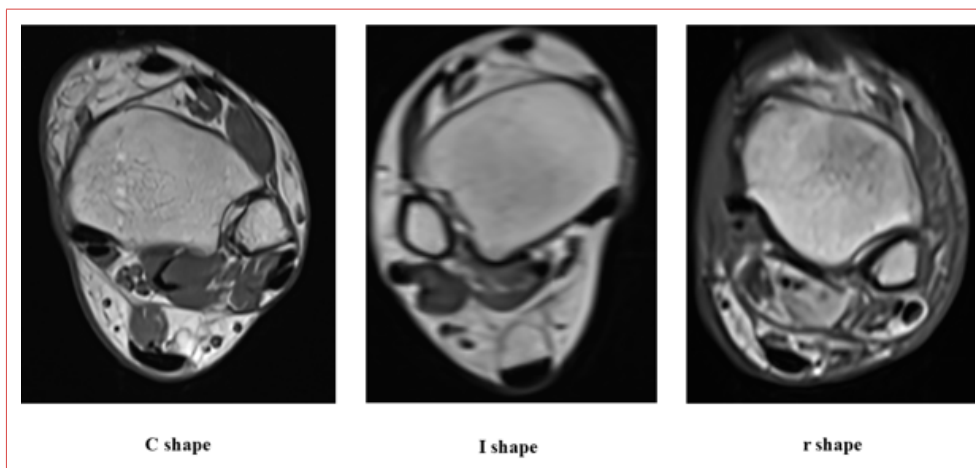


Figure 6. Representative axial magnetic resonance imaging examples of the three fibular notch morphology types: C-type (concave), I-type (shallow and flat), and r-type (rounded, with a smooth transition between the anterior and posterior tibial tubercles).

assessment, a randomly selected subgroup of 30 patients was re-evaluated by the first observer after a 3-week interval. Intraobserver and interobserver reliability for continuous measurements was assessed using intraclass correlation coefficients (ICC; two-way mixed-effects model, absolute agreement, single measures). Agreement for the categorical fibular notch morphology classification was evaluated using Cohen's kappa (κ). Interobserver agreement for the ordinal Schneck grading of ATFL injury was assessed using weighted Cohen's kappa based on the observers' initial independent ratings before consensus.

Potential Sources of Bias

Several potential sources of bias were considered. Selection bias may arise from the grade-stratified sampling design, in which a fixed number of patients were drawn at random from each Schneck grade; this design was adopted to maximize the efficiency of the ordinal model and precludes any inference about the population prevalence of injury grades or the absolute risk associated with a given morphological feature. A further source of selection bias is that only patients referred for MRI after an acute lateral ankle sprain were eligible, so that clinically mild sprains managed without advanced imaging are likely to be under-represented; the single-center tertiary setting may additionally limit generalizability. To minimize measurement bias, ATFL grading and morphological measurements were performed by separate observer pairs; all observers were blinded to the clinical data and to the findings of the other pair; all measurements were performed digitally on millimetrically calibrated PACS images, the mean of two independent measurements was used for each continuous parameter, and intraobserver and interobserver reliability was quantified. Residual confounding cannot be excluded: Age and injury side were included as pre-specified adjustment covariates, but limb dominance, level and type of physical activity, injury mechanism, concomitant CFL involvement, and the interval between trauma and MRI were not available from the retrospective records and could therefore not be modeled.

Statistical Analysis

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation for normally distributed data and as median (25th–75th percentile) for non-normally distributed data, in accordance with the test applied to each variable, and categorical variables as number (percentage). The Shapiro–Wilk test and histogram inspection were used to assess the normality of data distribution. Comparisons across the four ATFL injury grades were conducted using one-way analysis of variance (ANOVA) or the Kruskal–Wallis H test,

depending on normality. When significant differences were identified, Bonferroni-corrected post hoc tests were applied for ANOVA and Dunn–Bonferroni post hoc tests for Kruskal–Wallis analyses. Because 18 morphological parameters were compared across injury groups, p-values were adjusted using the Benjamini–Hochberg false discovery rate procedure, and significance was defined as $q < 0.05$. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. To evaluate independent associations between morphological parameters, clinical variables, and the ordinal severity of ATFL injury, an ordinal logistic regression model (proportional odds model) was used. Morphological variables with a p-value below 0.05 in univariate comparisons were considered candidate predictors for the multivariable model. Age and injury side were included as pre-specified adjustment covariates regardless of their univariate p-values. Before fitting the final model, candidate predictors were assessed for multicollinearity, geometric redundancy, and compliance with the proportional odds assumption. Variables with a variance inflation factor (VIF) > 5 were excluded because of multicollinearity. The tibiotalar sector angle was excluded because it is geometrically derived from the same best-fit circle as the talar radius. Fibular notch version was excluded because inclusion of this variable resulted in violation of the proportional odds assumption. All remaining candidate predictors and the pre-specified adjustment covariates were entered simultaneously into the final ordinal logistic regression model; no automated stepwise or backward elimination procedure was used. The proportional odds assumption for the final model was verified using the test of parallel lines. For univariate comparisons of morphological parameters, statistical significance was defined as an FDR-adjusted q value below 0.05; for all other analyses, a two-tailed p value below 0.05 was considered significant. No data were missing for any variable.

No artificial intelligence tools or large language models were used in any phase of this study, including study design, data collection, image analysis, statistical analysis, manuscript preparation, or language editing.

RESULTS

Study Population

A total of 280 patients (155 females, 125 males) were included in the final analysis. The median age of the cohort was 44.0 years (25th–75th percentile, 29.0–55.0; range, 18–84), and the median BMI was 27.8 kg/m² (25th–75th percentile, 25.0–30.1). The right and left ankles were affected in equal proportions (140 each). By design, each of the four Schneck grades comprised 70 patients (25.0%). Age, BMI, sex, and side did not differ significantly across the four injury grades (Table 1).

Table 1. Demographic characteristics according to ATFL injury grade

Variable	Grade 0 (n=70)	Grade I (n=70)	Grade II (n=70)	Grade III (n=70)	p
Age (years) ^a	41.0 (25.8–54.5)	42.0 (31.8–49.0)	48.0 (32.8–59.3)	48.0 (32.0–54.3)	0.054
BMI (kg/m ²) ^a	28.3 (25.2–30.6)	27.9 (24.3–29.7)	27.8 (25.1–30.5)	27.6 (25.2–30.1)	0.813
Sex (F/M) ^b	37/33	43/27	36/34	39/31	0.645
Side (R/L) ^b	37/33	31/39	29/41	43/27	0.077

Continuous variables are presented as median (25th–75th percentile) and categorical variables as counts. ^aKruskal–Wallis H test. ^bChi-square test. BMI: Body mass index; F: Female; M: Male; R: Right; L: Left; ATFL: Anterior talofibular ligament

Fibular Notch Morphology

The distribution of fibular notch morphology differed significantly across injury grades ($\chi^2=13.50$, $df=6$, $p=0.036$). The proportion of C-type notches increased progressively from grade 0 to grade III, whereas the proportion of I-type notches declined from 22.9% in grades 0 and I to 7.1% in grade III (Table 2).

Morphological Parameters

Nine of the 18 morphological parameters differed significantly across injury grades after false discovery rate correction (Table 3). Talar radius decreased progressively from grade 0 to grade III (19.54 → 17.22 mm, $q<0.001$), and anterior tubercle length increased progressively (11.41 → 12.44 mm, $q=0.038$). Tibiotalar sector angle ($q<0.001$), talar height ($q=0.007$), DTLA ($q=0.027$), and TD-FD ($q=0.027$) did not change monotonically but had higher median values in grades II and III than in grades 0 and I. Lateral/medial malleolar ratio ($q=0.007$), fibular notch version ($q=0.009$), and MML ($q=0.027$) also differed significantly, without a consistent trend across grades. TCA, fibular notch depth, TCoA, posterior tubercle length, LML, TCaIA, fibular position, APFA, and FTA did not differ significantly ($q>0.05$).

Pairwise Comparisons

Post hoc analysis showed that the main separation occurred between grades without fiber discontinuity (grades 0 and I) and those with a tear (grades II and III). Tibiotalar sector angle did not differ between grades 0 and I ($p=1.000$) or between grades II and III ($p=1.000$), but differed significantly across this boundary (grade 0 vs II, $p<0.001$; grade I vs II, $p=0.002$). A

similar but incomplete pattern was observed for talar height and TD-FD. Apart from fibular notch version, which followed a non-monotonic course across grades, talar radius was the only parameter that also separated grade 0 from grade I ($p=0.004$), being highest in patients with a fully intact ligament.

Multivariable Analysis

Assessment of multicollinearity identified variance inflation factors above 5 for MML (12.45), lateral/medial malleolar ratio (12.08), and LML (5.44), reflecting the arithmetic dependence between the ratio and its components; these variables were excluded from the multivariable model. All remaining predictors had variance inflation factors below 1.7. Fibular notch version was excluded because the proportional odds assumption was not satisfied when it was included in the model (test of parallel lines, $\chi^2=36.10$, $df=18$, $p=0.007$), and the tibiotalar sector angle was excluded because it is geometrically derived from the same best-fit circle as the talar radius.

The ordinal logistic regression model was statistically significant ($\chi^2=87.29$, $df=9$, $p<0.001$; Nagelkerke $R^2=0.286$), and the test of parallel lines was consistent with the proportional odds assumption ($\chi^2=12.61$, $df=18$, $p=0.814$). A smaller talar radius (OR=0.761/mm, $p<0.001$), a greater talar height (OR=1.095/mm, $p<0.001$), a higher DTLA (OR=1.112 per degree, $p=0.004$), a longer anterior tubercle (OR=1.183/mm, $p=0.004$), and a greater TD-FD (OR=1.428/mm, $p=0.003$) were independently associated with a higher ATFL injury grade. An I-type fibular notch was associated with markedly lower odds of a higher grade than a C-type notch (OR=0.295, $p<0.001$), whereas the r-type did not differ from the C-type (OR=0.693, $p=0.209$).

Table 2. Distribution of fibular notch morphology according to ATFL injury grade

Morphology	Grade 0 (n=70)	Grade I (n=70)	Grade II (n=70)	Grade III (n=70)	χ^2	df	p
C-type	37 (52.9)	44 (62.9)	47 (67.1)	53 (75.7)	13.504	6	0.036
I-type	16 (22.9)	16 (22.9)	8 (11.4)	5 (7.1)			
r-type	17 (24.3)	10 (14.3)	15 (21.4)	12 (17.1)			

Values are n (%). Chi-square test. Linear-by-linear association: $\chi^2=4.180$, $df=1$, $p=0.041$. ATFL: Anterior talofibular ligament

Table 3. Radiographic and MRI-based morphological parameters according to ATFL injury grade

Parameter	Grade 0 (n=70)	Grade I (n=70)	Grade II (n=70)	Grade III (n=70)	p	q	Significant pairwise comparisons
Talar morphology							
Talar radius (mm) ^a	19.54±2.84	17.99±3.33	17.52±1.85	17.22±2.39	<0.001	<0.001	0 versus I, 0 versus II, 0 versus III
Tibiotalar sector angle (°) ^b	80.34 (71.00–85.30)	79.00 (74.00–86.12)	87.30 (79.72–95.58)	87.10 (82.00–95.33)	<0.001	<0.001	0 versus II, 0 versus III, I versus III
Talar height (mm) ^b	31.05 (28.07–35.23)	32.10 (28.25–34.00)	34.40 (30.48–37.58)	33.65 (31.25–37.62)	0.001	0.007	0 versus III, I versus II, I versus III
Talar convexity angle (°) ^b	108.00 (102.00–113.25)	108.00 (103.00–114.25)	105.00 (97.75–115.25)	103.00 (97.75–114.00)	0.129	0.193	—
Fibular notch morphology							
Fibular notch version (°) ^b	32.70 (29.30–37.20)	31.40 (17.50–34.08)	30.85 (26.93–34.55)	32.75 (29.77–37.12)	0.002	0.009	0 versus I, I versus III
Anterior tubercle length (mm) ^a	11.41±2.03	11.77±1.53	12.02±2.21	12.44±2.08	0.019	0.038	0 versus III
Fibular notch depth (mm) ^b	3.75 (3.48–3.90)	3.71 (3.52–3.86)	3.78 (3.56–4.05)	3.75 (3.50–4.09)	0.107	0.174	—
Posterior tubercle length (mm) ^b	11.30 (10.20–12.00)	11.55 (10.07–12.43)	11.70 (10.88–13.53)	11.70 (10.40–14.10)	0.146	0.202	—
AP tubercle angle (°) ^b	138.00 (128.55–149.45)	137.80 (129.38–152.00)	138.55 (130.35–146.43)	135.60 (127.50–142.78)	0.347	0.367	—
Ankle mortise and malleolar morphology							
Lateral/medial malleolar ratio ^b	2.34 (1.84–2.95)	2.12 (1.86–2.53)	2.29 (1.96–2.78)	2.74 (2.07–3.00)	0.002	0.007	I versus III
Distal tibial lateral angle (°) ^b	89.45 (87.28–91.12)	88.90 (88.00–91.20)	90.75 (88.15–92.65)	90.35 (88.45–92.62)	0.012	0.027	—
Medial malleolar length (mm) ^b	10.45 (8.88–13.10)	12.00 (10.20–13.62)	11.55 (9.22–13.03)	10.25 (8.80–11.53)	0.012	0.027	I versus III
Talar dome–distal fibula distance (mm) ^b	3.30 (2.80–4.10)	3.25 (2.67–3.85)	3.70 (3.17–4.28)	3.55 (3.10–4.10)	0.010	0.027	I versus II
Talocrural angle (°) ^b	16.10 (11.32–18.02)	16.00 (12.38–18.30)	14.90 (11.28–17.48)	16.20 (13.88–18.70)	0.067	0.120	—
Lateral malleolar length (mm) ^b	26.20 (23.98–28.93)	25.60 (23.18–28.02)	26.65 (24.02–29.50)	27.05 (24.77–30.00)	0.158	0.203	—
Fibular position (%) ^a	30.35±9.58	28.61±8.36	31.32±11.15	31.47±10.21	0.293	0.330	—
Hindfoot alignment							
Talocalcaneal angle (°) ^a	35.19±6.75	34.27±6.30	36.73±8.01	35.17±6.26	0.202	0.242	—
Fibulotalar angle (°) ^b	131.00 (124.75–143.00)	130.55 (123.00–141.22)	134.00 (119.75–141.25)	134.50 (120.75–145.25)	0.872	0.872	—

Values are presented as mean±SD for variables analyzed using one-way ANOVA and as median (25th–75th percentile) for variables analyzed using the Kruskal–Wallis H test. ^aOne-way ANOVA with Bonferroni *post hoc* comparisons; ^bKruskal–Wallis H test with Dunn–Bonferroni *post hoc* comparisons. q=Benjamini–Hochberg false discovery rate–adjusted p-value across the 18 parameters tested; significance was defined as q<0.05. *Post hoc* pairwise comparisons are reported only for parameters that remained significant after false discovery rate correction (q<0.05). — Indicates no significant pairwise difference. ATFL: Anterior talofibular ligament, MRI: Magnetic resonance imaging.

Table 4. Multivariable ordinal logistic regression model for anterior talofibular ligament injury grade

Variable	OR	95% CI	p
Talar radius (per mm)	0.761	0.696–0.832	<0.001
Talar height (per mm)	1.095	1.047–1.145	<0.001
Distal tibial lateral angle (per degree)	1.112	1.036–1.195	0.004
Anterior tubercle length (per mm)	1.183	1.055–1.327	0.004
Talar dome–distal fibula distance (per mm)	1.428	1.124–1.811	0.003
Fibular notch morphology: l-type (ref. C-type)	0.295	0.154–0.564	<0.001
Fibular notch morphology: r-type (ref. C-type)	0.693	0.392–1.228	0.209
Side: right (ref. left)	1.519	0.973–2.370	0.066
Age (per year)	1.006	0.992–1.020	0.404

Model $\chi^2=87.29$, $df=9$, $p<0.001$; Nagelkerke $R^2=0.286$ (Cox–Snell $R^2=0.268$; McFadden $R^2=0.112$). Test of parallel lines: $\chi^2=12.61$, $df=18$, $p=0.814$. Threshold estimates: grade 0, 9.688; grade I, 11.094; grade II, 12.459. Reference category for injury side is the left ankle, and for fibular notch morphology, the C-type notch. Odds ratios above 1 indicate higher odds of a more severe injury grade. OR: Odds ratio, CI: Confidence interval

Neither injury side (OR=1.519, 95% confidence interval [CI]: 0.973–2.370, $p=0.066$) nor age (OR=1.006, $p=0.404$) was independently associated with injury grade (Table 4).

Reliability

Intraobserver ICC values for continuous morphological measurements ranged from 0.87 to 0.97, and interobserver ICC values ranged from 0.82 to 0.95, indicating good to excellent reliability. Interobserver agreement for fibular notch morphology classification was substantial ($\kappa=0.79$). Interobserver agreement for Schneck grading of ATFL injury was also substantial (weighted $\kappa=0.75$).

DISCUSSION

The principal finding of this study is that osseous morphology at the level of the talocrural joint is independently associated with the severity of acute ATFL injury. In a balanced cohort of 280 patients distributed evenly across the four Schneck grades, a smaller talar radius, a greater talar height, a higher DTLA, a longer anterior tubercle of the fibular notch, a greater TD-FD, and a C-type rather than an l-type fibular notch were each independently associated with a higher injury grade. The model showed modest overall explanatory performance (Nagelkerke $R^2=0.286$), suggesting that osseous morphology represents only one component of the multifactorial mechanisms associated with ligament injury severity.

This finding must be placed in a conflicting literature. Frigg et al. reported the opposite direction, with a larger talar radius in patients with CAI (21.2 ± 2.4 mm) than in controls (17.7 ± 1.9 mm), and interpreted a larger radius as producing a flatter dome with reduced tibial restraint.^[22] Zendeli et al., in contrast, found a smaller talar radius in patients with recurrent instability after

a modified Broström–Gould procedure, and attributed the discrepancy to the fact that the earlier measurements were not normalized to body height, which may have introduced bias because taller patients have both larger talar width and larger radii.^[23] Three-dimensional analyses of talar articular geometry have found no difference in curvature between patients with chronic instability and controls.^[13] Our values (17.2–19.5 mm) fall within the range reported for controls rather than for the instability group,^[22] and our direction of effect is consistent with that of Zendeli et al.^[23] Direct numerical comparison with that study nevertheless remains limited, because they normalized the talar dimensions to body height whereas the present measurements are reported in absolute units; radiographic technique, however, was comparable, as both studies used weight-bearing views.

The tibiotalar sector angle showed the reverse relationship, increasing from a median of 80.34° in grade 0 to 87.10° in grade III. Within our data, this is internally coherent: a smaller best-fit circle subtends a larger angle at the same plafond width, so a decreasing radius and an increasing sector angle describe the same geometry. However, both Frigg et al.^[22] and Zendeli et al.^[23] reported a smaller tibiotalar sector in unstable ankles, the latter with a marked difference (69.8° vs. 79.3°). Our finding therefore contradicts the prevailing interpretation that reduced bony containment predisposes to lateral ligament failure.

Two explanations should be considered. First, the populations differ: previous studies examined chronic instability or recurrent instability after surgery,^[22,23] whereas the present cohort comprised acute sprains, and our comparison group consisted of patients who had also sustained an inversion

injury but retained an intact ligament. Second, and more speculatively, greater osseous containment may transfer a larger proportion of the inversion load to the ligamentous restraints rather than allowing it to dissipate through talar rotation within the mortise. This hypothesis is consistent with our data but cannot be tested in a cross-sectional design and requires biomechanical confirmation.

An I-type (shallow) notch was associated with substantially lower odds of a higher injury grade than a C-type notch ($OR=0.295$). The proportion of I-type notches fell from 22.9% in grades 0 and I to 7.1% in grade III. This is the opposite of what would be predicted from the syndesmotic literature, in which a shallow incisura has been linked to a higher incidence of ligamentous ankle injury, although the corresponding systematic review emphasised that not all studies confirmed this association and that methodology was heterogeneous.^[11]

The TD-FD was independently associated with a higher injury grade in the multivariable model ($OR=1.428/mm$), with wider distances observed in the higher injury grades. This measurement reflects the width of the lateral gutter, that is, the transverse clearance between the talus and the fibula, and a wider gutter is generally interpreted as reduced lateral osseous constraint permitting greater talar tilt during an inversion moment. At first sight this appears to conflict with the sector angle finding described above, in which greater rather than lesser osseous containment accompanied higher injury grades. The two measurements, however, describe different planes: the tibiotalar sector angle quantifies sagittal coverage of the talar dome by the tibial plafond, whereas the TD-FD quantifies transverse clearance at the lateral gutter. A configuration combining extensive sagittal coverage with a wide lateral gutter would constrain sagittal translation while permitting coronal tilt, and would therefore be expected to load the ATFL preferentially. This interpretation is consistent with the present data but was not tested directly and requires biomechanical confirmation.

Fibular notch depth, measured as a continuous variable, did not differ across grades ($q=0.174$), and notch depth did not distinguish the three morphological types in our cohort. This mirrors the observation of Mısırlı et al., who defined the same three types partly by a 4 mm depth threshold yet found no difference in measured depth between them.^[20] Taken together, these observations suggest that morphological type and quantitative notch depth capture different aspects of incisura anatomy and should not be treated as interchangeable.

Fibular notch version was higher in grade III than in grade I, in the same direction reported by Yaka et al. in patients with ATFL rupture.^[24] Our absolute values were approximately

twice theirs, which reflects a difference in the reference line used and precludes direct numerical comparison. Notably, the median version angle was lowest in grade II rather than in grade 0, and when it was included in the multivariable model the proportional odds assumption was no longer satisfied (test of parallel lines, $p=0.007$); it was therefore excluded. This non-monotonic behavior should be interpreted with caution.

Post hoc comparisons revealed a consistent pattern: for the tibiotalar sector angle, and partially for talar height and TD-FD, grades 0 and I did not differ from each other, grades II and III did not differ from each other, but the two pairs differed significantly. The morphological signal therefore separates ankles in which the ligament remained continuous from those in which fibre discontinuity occurred, rather than grading the extent of the tear. Apart from fibular notch version, whose course across grades was non-monotonic, only talar radius separated grade 0 from grade I. This distinction matters for interpretation: our data support an association between osseous morphology and whether the ATFL tears, and provide weaker evidence that morphology determines how extensively it tears.

Given the modest explanatory performance of the model (Nagelkerke $R^2=0.286$), these parameters should not be used to predict injury severity in an individual patient. Their potential value lies at the level of hypothesis generation rather than clinical application. Talar radius, talar height, and TD-FD are obtainable from routine radiographs without additional acquisitions, and it is conceivable that a patient with recurrent inversion injuries who shows a small talar radius, a greater talar height, and a wide lateral gutter might benefit from a lower threshold for structured proprioceptive rehabilitation or bracing. This possibility is speculative: the present study was cross-sectional, did not assess prospective injury risk, recurrence, treatment response, or functional outcomes, and therefore cannot support any anatomy-based treatment recommendation. Prospective studies with clinical endpoints would be required before such an approach could be considered.

Patients were sampled to obtain balanced groups across Schneck grades; the study sample therefore does not reflect the population prevalence of ATFL injury grades, the reported group proportions should not be interpreted as prevalence estimates, and the design does not permit estimation of absolute injury risk associated with any morphological feature. The findings should accordingly be interpreted as associations between morphological characteristics and ATFL injury grade rather than as individual-level predictions. The study is further limited by its retrospective, single-center design, which may restrict generalizability. Functional and clinical stability assessments were not included; therefore, direct correlation

between morphology and functional outcomes could not be analyzed. Minor variations in radiographic projection or ankle positioning may have influenced some measurements. The TCoA has previously been reported to show only moderate interobserver reliability,^[19] which should be considered when interpreting this parameter. The absence of a healthy control group limits differentiation between normal anatomical variations and predisposing risk factors. Mechanism of injury, concomitant CFL involvement, and the interval between trauma and MRI were not recorded, and these factors may influence injury severity independently of osseous morphology. The raw linear measurements were analysed in absolute units and were not normalized for body height or foot size; because larger individuals have proportionally larger tarsal dimensions, part of the observed variation in the talar and malleolar measurements may reflect overall body size rather than a configuration specific to ligament injury. Finally, all measurements were performed on two-dimensional images; three-dimensional evaluation could provide more precise morphometric data.

CONCLUSION

Osseous morphology at the talocrural joint is independently associated with the severity of acute ATFL injury. A smaller talar radius, a greater talar height, a higher DTLA, a longer anterior tubercle of the fibular notch, a greater TD-FD, and a C-type rather than an I-type notch configuration were each independently associated with higher injury grades, and the association was driven mainly by the distinction between ligaments that remained continuous and those that tore. These parameters are obtainable from routine radiographs and MRI and may contribute to anatomy-informed risk assessment; however, given the modest explanatory performance of the multivariable model, they should not be regarded as predictors of individual outcomes.

Disclosures

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (No: 5097, Date: 30/09/2025).

Informed Consent: Written informed consent was obtained from all individual participants included in the study.

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