2025 MARCH VOL 8 ISSUE 1

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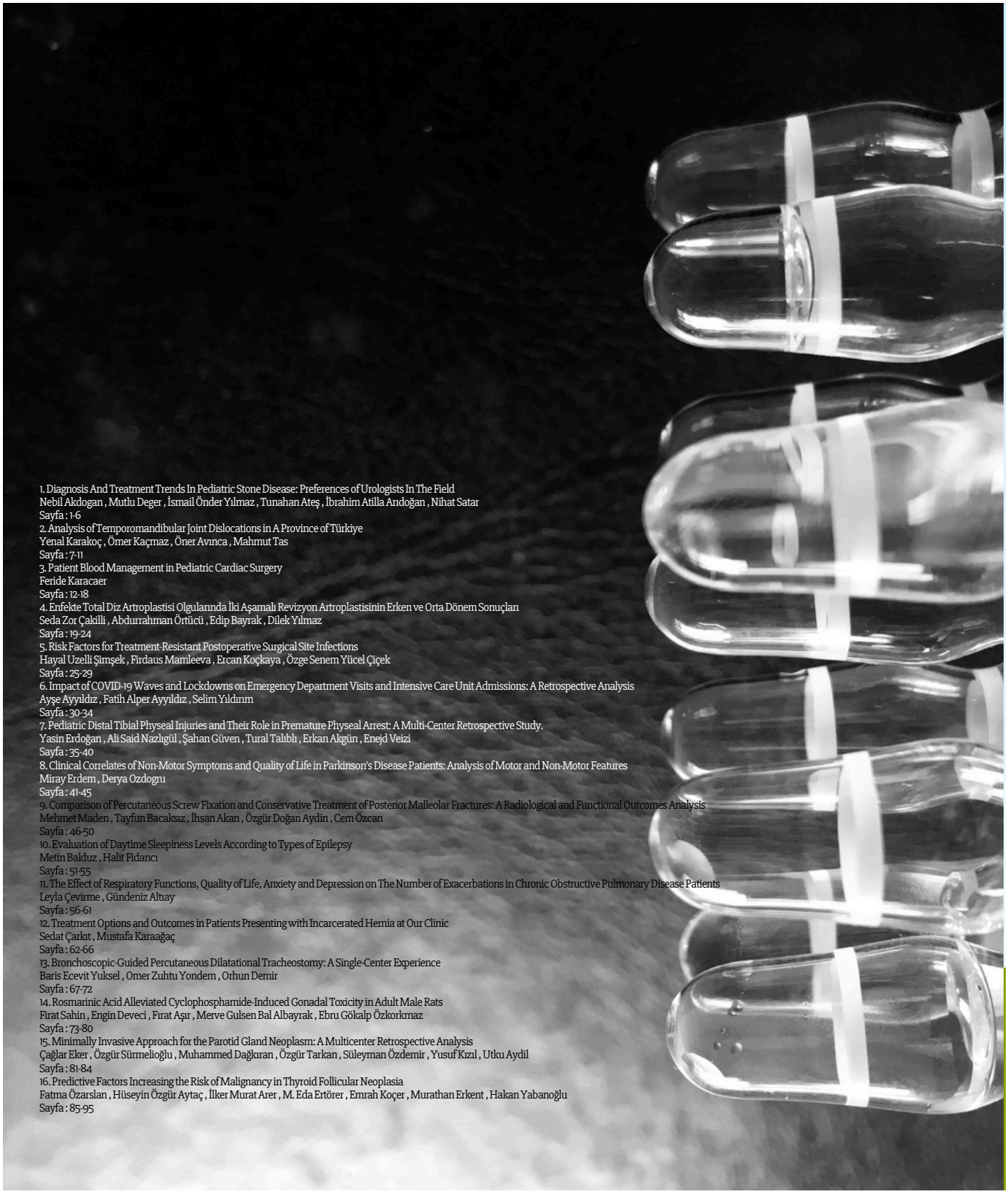

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ABSTRACTED & INDEXED

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BASE
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ASOS Indeks
Türkiye Atıf Dizini

AIM

The aim of the journal is to announce offering of national and international scientific environment and share high quality research studies, case studies and reviews conducted in the field of anesthesia, pain medicine, intensive care and surgical sciences both in Turkey and abroad; and to contribute to the development of scientific communication by establishing a continuous educational platform.

SCOPE

Çukurova Anestezi ve Cerrahi Bilimler Dergisi (J Cukurova Anesth Surg) is published online three times a year (April, August, December). Special or supplement series may also be published where necessary. Manuscripts submitted to the journal are evaluated by independent peer reviews according to double blind peer review system. Scientifically reviewed manuscripts can be freely accessed through the internet without financial, legal and technical barriers. These manuscripts can be read, downloaded, copied, distributed, printed, scanned, linked to full texts, indexed, transferred as data to the software and used for any legal purpose. Authors and copyright owners agree that all users have freeaccess.
All scientific papers sent to the Çukurova Anestezi ve Cerrahi Bilimler Dergisi should take into account the recommendations of the International Committee of Medical Journal Editors and the International Standards for Editors (ICJME) and Authors of the Committee on Publication Ethics(COPE).

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Selahattin Eyyubi Mahallesi, Şht. Jnd. Er Gökhan Yılmaz Cd. No:142, 01240 Yüreğir/Adana
+905317936241
anestezidergisi@gmail.com
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ETHICAL PRINCIPLES & PUBLICATION POLICY I

Scientific Responsibility

In terms of scientific publishing standards, the articles to be submitted should be prepared in accordance with the criteria of the International Medical Journal Editors Board (ICMJE), Publication Ethics Committee (COPE).
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• Articles should not have been published anywhere before and / or should not be in the evaluation process for publication.
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Ethical Responsibility

• Compliance with the Helsinki Declaration Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) is sought in all studies involving the element of "Human". In such studies, the authors should state that they carried out the study in accordance with these principles in the MATERIAL AND METHODS section, and that they received approval from the ethics committees of their institutions and "informed consent" from the people who participated in the study.
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• Authors are responsible for reporting all personal and financial relationships related to the study. It must be clearly declared whether there is any conflict of interest associated with the application and / or evaluation of the article.
• The authors are responsible for the compliance of the articles with scientific and ethical rules.

1. Authors

Authors must comply with all authorship policies and conflict of interest statements detailed in Sections IIA and B of this document.

a. Predatory or Fake Journals

These are called predatory journals because of the rapidly increasing numbers of journals called 'scientific journals' but that publish all the posts for a fee without any screening for profit. It has become more important to maintain some standards in scientific journalism. For this reason, our journal follows the recommendations of organizations such as ICMJE, COPE and WAME and complies with the standards.

2. Journals

a. security

Manuscripts submitted to journals are privileged communications that are the private, confidential property of the author, and authors can be harmed by premature disclosure of any or all the details of a manuscript.
For this reason, editors should not share with anyone other than the authors and reviewers whether it has been handled and reviewed, its content and status in the review process, including the reviewers' critique and eventual fate. Requests from third parties to use reviews in manuscripts and legal proceedings should be politely refused, and editors should do their best not to provide such confidential material as subpoenas.
Editors should also make it clear that the reviewers must keep the manuscripts, related materials, and information they contain strictly confidential.
Reviewers and editorial staff should not publicly discuss the author's work, and reviewers should not endorse the ideas of the authors prior to publication. Reviewers should not keep the article for their personal use and should destroy the hard copies of the articles and delete the soft copies after submitting their reviews.
When an article is rejected, it is best practice for journals to delete copies from their editorial systems unless local regulations require retention.
Journals that maintain copies of rejected manuscripts should disclose this practice in the Authors' Notice.
When an article is published, journals should retain copies of the original submission, review, revision, and correspondence for at least three years, and possibly permanently, depending on local regulations, to answer future questions about the work.
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Confidentiality may need to be breached if fraud or alleged fraud is present, but editors notify authors or reviewers of their willingness to do so, and confidentiality should be honored otherwise.

b. Timing

Editors should do their best to ensure that manuscripts are processed in a timely manner with the resources available to them. If editors are going to publish an article, they should try to do it on time and planned delays should be negotiated with the authors. If a journal has no intention of continuing an article, editors should try to reject the article as soon as possible to allow the author to submit it to a different journal.

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ETHICAL PRINCIPLES & PUBLICATION POLICY II

c. Peer Review

Peer review is a critical evaluation of manuscripts submitted to journals by experts who are not usually part of the editorial staff. Peer review is an important extension of the scientific process, as impartial, independent, critical evaluation forms the core of all scientific work, including scientific research.

The true value of peer review is debated, but the process facilitates a fair hearing for an article among members of the scientific community. More practically, it helps editors decide which articles are appropriate for their journal. Peer review often helps authors and editors improve the quality of their reporting.

It is the editor's responsibility to ensure that reviewers have access to all material related to the review of the manuscript, including additional material for email-only, for selection of appropriate reviewers, and to ensure that reviewer reviews are appropriately evaluated and interpreted in context.

A peer-reviewed journal is not obligated to submit articles submitted for review and is not obligated to follow up on reviewers' suggestions, positive or negative. The editor of a journal is ultimately responsible for the selection of all content, and editorial decisions may be made aware of matters unrelated to the quality of a manuscript, such as journal relevance. An editor may reject any article at any time, including after it has been accepted when concerns about the integrity of the work arise.

Journals may differ in the number and types of articles they submit for review, the number and types of reviewers they seek for each article, whether the review process is open or blind, and other aspects of the review process. For this reason, and as a service to authors, journals should publish a description of the peer review process.

Journals should ultimately review their decision to accept or reject a paper and acknowledge the reviewers' contribution to their journals. Editors are encouraged to share reviewers' comments with reviewers of the same article so that reviewers can learn from each other during the review process.

As part of peer-review, editors are encouraged to review research protocols, statistical analysis plans if separate from the protocol, and/or contracts related to project-specific studies. Editors should encourage authors to make such documents public at the time of or after publication before accepting such work for publication. Some journals may require these documents to be publicly posted as a condition of their acceptance.

Log requirements for independent data analysis and availability of publicly available data were published during this revision; this reflects evolving views on the importance of data availability for pre- and post-publication peer review. Some journal editors currently request statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others encourage or request authors to share their data with others for review or reanalysis, while others indicate whether study data may be used by third parties for viewing and/or reanalysis. Each journal should establish and publish its own specific requirements for data analysis and registration in a place easily accessible to potential authors.

Some people believe that true scientific peer review only begins when a paper is published. In this regard, medical journals should have a mechanism for readers to submit comments, questions or criticisms on published articles, and authors should respond appropriately and cooperate with requests for journal data or request additional information regarding the paper. occurs after publication (see Chapter III).

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and its contribution to the evidence for its originality, quality, and important questions. These decisions should not be influenced by business interests, personal relationships, or agendas, or by findings that are negative or credibly question accepted wisdom. In addition, authors should submit for publication or make it publicly available, and editors should not consider publication, exclude studies with findings that are not statistically significant or have inconclusive findings. Such studies may provide evidence that evidence pooled with other studies through meta-analysis can still help answer important questions, and public recording of such negative or inconclusive findings may prevent unintended duplication of effort or other researchers considering similar studies. can be valuable to Journals should clearly outline the appeals process and have a system in place to respond to appeals and complaints.

e. Journal Metrics

Journal impact factor is widely misused as a proxy for research and journal quality and as a measure of the benefits of research projects or individual researchers, including their eligibility for recruitment, promotion, hiring, awards, or research funding. The ICMJE recommends that journals reduce the emphasis on impact factor as a single measure, instead offering a set of articles and journal metrics related to their readers and authors.

3. Reviewers

Manuscripts submitted to journals are privileged communications that are the private, confidential property of the author, and authors may suffer from early disclosure.

Therefore, the reviewers should keep the articles and the information they contain strictly confidential. Reviewers should not publicly discuss the author's work and properly write down the authors' ideas before the article is published. Reviewers should not keep the article for their personal use and should destroy the copies of the articles after reviewing them.

Reviewers are expected to respond promptly to review requests and submit reviews within the agreed timeframe. Reviewers' comments should be constructive, honest, and polite.

Reviewers must declare conflicts of interest and withdraw themselves from peer review if there is a conflict.

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The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" are committed to publishing only original material, i.e., material that has neither been published elsewhere, nor is under review elsewhere.
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1. On policy

1.1. Every institution of higher education should have a policy assuring that peer-reviewed versions of all future scholarly articles by faculty members are deposited in the institution's designated repository. (See recommendation 3.1 on institutional repositories.)

- Deposits should be made as early as possible, ideally at the time of acceptance, and no later than the date of formal publication.
- University policies should respect faculty freedom to submit new work to the journals of their choice.
- University policies should encourage but not require publication in OA journals, and should help faculty understand the difference between depositing in an OA repository and publishing in an OA journal.
- When possible, university policies should be adopted by faculty vote, should require immediate OA, and should welcome repository deposits even when not required (e.g. datasets, conference presentations, books or book chapters, work published before the policy's adoption, and so on).
- When publishers will not allow OA on the university's preferred terms, we recommend either of two courses. The policy may require dark or non-OA deposit in the institutional repository until permission for OA can be obtained. Or the policy may grant the institution a nonexclusive right to make future faculty research articles OA through the institutional repository (with or without the option for faculty to waive this grant of rights for any given publication).

1.2. Every institution of higher education offering advanced degrees should have a policy assuring that future theses and dissertations are deposited upon acceptance in the institution's OA repository. At the request of students who want to publish their work, or seek a patent on a patentable discovery, policies should grant reasonable delays rather than permanent exemptions.

1.3. Every research funding agency, public or private, should have a policy assuring that peer-reviewed versions of all future scholarly articles reporting funded research are deposited in a suitable repository and made OA as soon as practicable.

- Deposits should be made as early as possible, ideally at the time of acceptance, and no later than the date of formal publication.
- When publishers will not allow OA on the funder's terms, funder policies should require grantees to seek another publisher.
- If funder policies allow embargoes before new work becomes OA, the embargoes should not exceed six months. Policies should allow no embargoes at all for uncopyrightable work.
- Funders should treat publication costs as research costs, and should help grantees pay reasonable publication fees at fee-based OA journals.
- When possible, funder policies should require libre OA, preferably under a CC-BY license or equivalent.
- A repository is suitable for this purpose when it provides OA, supports interoperability with other repositories, and take steps toward long-term preservation. The funder's choice should be determined by ongoing research into questions such as which choice best fosters the deposit of covered articles, the utility of deposits, the convenience of funders and authors, and incentives for the further growth of OA.

1.4. All university and funder OA policies should require deposit in a suitable OA repository between the date of acceptance and the date of publication. The metadata should be deposited as soon as it is available and should be OA from the moment of deposit. The full-text should be made OA as soon as the repository has permission to make it OA.

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The abstract should have a maximum length of 250 words. The Objective should include Materials and Methods, Results and Conclusion. Keywords with at least 3 (three) words should be written with a space between the abstract.
Research article format; Introduction, material and method, findings, discussion and conclusion
Case presentation format; Introduction, case report, history, tests, progress, treatment and outcome, discussion-literature review, recommendations
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If the name is not given in the sentence, the source number should be given in superscript before the pointYear, volume, start and end pages should be gn in journal sources, but only the year should be stated in book sources.
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STATISTICS

TIME STATISTICS, ACCEPTANCE-REJECTION STATISTICS LAST 3 YEARS

Year	Number of Accepted Articles	Number of Rejected Articles	Acceptance Ratio	Rejection Ratio
2022	56	20	%74	%26
2023	85	23	%79	%21
2024	56	15	%79	%21

Statistic	Number of Articles Calculated	Average Time (Day)
Article Submission - Withdraw:	5	12
Article Submission - Return:	3	46
Article Submission - First Editor Assignment:	72	8
First Editor Assignment - Acception Decision Statistic		
Peer review:	54	81
Non peer review:	0	0
First Editor Assignment - Rejection Decision Statistic		
Peer review:	7	41
Non peer review:	5	29
Article Submission - Acception Decision Statistic		
Peer Review:	54	88
Non Peer Review:	0	0
Article Submission - Rejection Decision Statistic		
Peer Review:	7	49
Non Peer Review:	5	32

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Diagnosis and Treatment Trends in Pediatric Stone Disease: Preferences of Urologists in the Field

Nebil Akdogan[1], Mutlu Deger[1], Ismail Onder Yılmaz[1], Tunahan Ates[2], Ibrahim Atilla Arıdogan[1], Nihat Satar[1]

1 Department of Urology, Faculty of Medicine, Cukurova University, Adana, Türkiye
2 Department of Urology, Defne State Hospital, Hatay, Türkiye

Abstract

Aim: Many different treatment options exist for pediatric stone disease (PSD). We conducted a survey among urologists in Turkey to find out which diagnostic and therapeutic methods urologists choose for stones of different localization and size in pediatric patients of varying age groups.

Methods: A survey on treatment options in various PSD was developed for urologists working in hospitals of different status. The survey consisted of 42 multiple-choice questions, and the average response time was 5 minutes. The measure taken to avoid repetitive responses was that the survey could only be completed once from an internet protocol.

Results: The number of respondents was 95. 91.67%, 89.47%, and 80.21% of the participants preferred ultrasonography as the diagnostic method in the 0-2, 2-6, and 6-18 age ranges, respectively. In treating staghorn kidney stones between 0-2 and 2-6 years, mini percutaneous nephrolithotomy (PCNL) was preferred most frequently, followed by standard PCNL. In all age groups, shockwave lithotripsy was the most common procedure for symptomatic pelvic stones smaller than 10 mm, followed by retrograde intrarenal surgery in the second frequency. Endoscopic surgery was the most preferred method for bladder stones smaller than 2 cm in all age groups.

Conclusion: The management of urinary tract stones in pediatric patients involves a complex set of processes. The sole aim is not to achieve stone-free management. Urologists in Turkey act following the guidelines. However, this is not always possible due to the lack of facilities. The necessary facilities for urologists need to be improved.

***Keywords**: Pediatric; stone disease; trend; urologist; survey*

1. Introduction

Pediatric stone disease (PSD) is a major problem in urology practice today. The incidence and characteristics of stones show wide geographical variation in children.[1] PSD is endemic in Turkey, Pakistan, and some South Asian, African, and South American countries. However, epidemiological studies have shown that the incidence of pediatric stone disease is also increasing in the Western world.[2–4] A major contributor to the morbidity associated with nephrolithiasis is disease recurrence. Stone recurrence increases the morbidity of nephrolithiasis. Pediatric patients constitute a high-risk patient population that because of followed carefully due to the risk of stone recurrence for many years.[5]

Therefore, postoperative follow-up and treatment management are also of great importance. It is known that 25-50% of children with nephrolithiasis undergo surgical intervention.[6,7] Common procedures for nephrolithiasis include extracorporeal shockwave lithotripsy (SWL), retrograde intrarenal surgery (RIRS) with ureteroscopy (URS), and percutaneous nephrolithotomy (PCNL). Open, laparoscopic, and robot-assisted laparoscopic surgery are rare and performed in selected patient groups.[1] With the advancement of technology, stone management has shifted from open surgical approaches to less invasive endoscopic techniques. Treatment depends on the number, size, location, type, and anatomy of the urinary tract.[8,9]

There are many different treatment options for urinary tract stones. The majority of urologists intervene in urinary tract stones in adult patients. However, this may differ in pediatric patients. Therefore, we conducted a survey among urologists in Turkey to find out which diagnostic and therapeutic methods urologists choose for stones of different localization and size in pediatric patients of varying age groups.

Corresponding Author: Tunahan Ates, drtunahanates0101@gmail.com, Received: 06.10.2024, Accepted: 18.12.2024, Available Online Date: 15.03.2025 Cite this article as: Akdogan T, Deger M, Yılmaz IO, Ates T, Arıdogan IA, Satar N. Diagnosis and Treatment Trends In Pediatric Stone Disease: Preferences of Urologists In The Field. J Cukurova Anesth Surg. 2025; 8(1): 1-6. https://doi.org/10.36516/jocass.1562263

2. Materials and Methods

The study was conducted in compliance with the principles of the Declaration of Helsinki and additional approval was obtained from the Ethics Committee of Çukurova University, Medical Faculty, Adana, Turkey (2023-138/63).

Based on the EAU (European Association of Urology) 2023 guidelines [1,10] for various forms of PSD, a survey on treatment options in various PSD was developed for urologists working in hospitals of different status. The survey included the title and experience of the urologist in charge. The respondents were also asked about the imaging modalities used in different age groups and the treatment modalities for kidney stones (pelvis, lower pole calyx, staghorn), ureteral stones (upper and lower), and bladder stones.
The survey consisted of 42 multiple-choice questions (**Table 1)**, and the average response time was 5 minutes. The measure taken to avoid repetitive responses was that the survey could only be completed once from an internet protocol address.

After ethics committee approval the survey was sent to urologists nationwide via e-mail and mobile application. Participants' responses were then collected and analyzed. Categorical variables were expressed as numbers and percentages. The chi-square test was used to compare categorical variables between groups. All analyses were performed using IBM (Armonk, NY, USA) SPSS Statistics Version 20.0 statistical software. The level of statistical significance for all tests was set as $p < 0.05$.

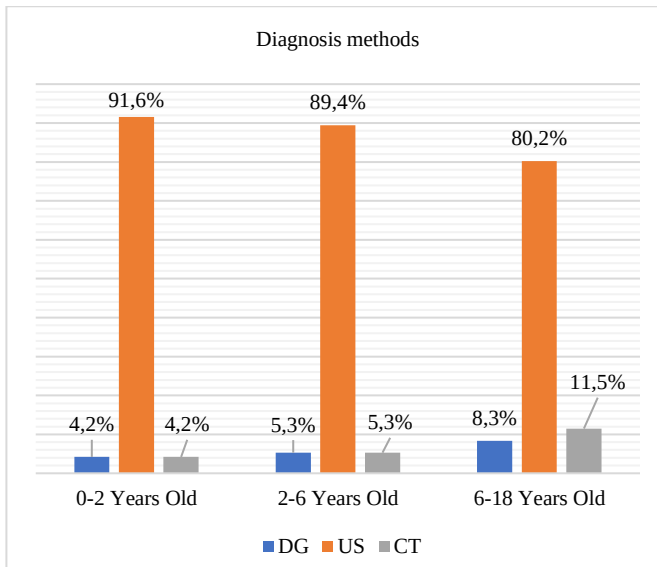
Table 1

The questions asked in the survey

1. What is your title?
2. Where do you work?
3. How many years are you in your profession?
4. Have you done a minor in pediatric urology?
5. In your daily practice, which imaging modality do you prefer first for diagnostic purposes in pediatric stone patients aged 0-2 years?
6. In your daily practice, which imaging method do you prefer first for diagnostic purposes in pediatric stone patients aged 2-6 years?
7. In your daily practice, which imaging method do you prefer first for diagnostic purposes in pediatric stone patients aged 6-18 years?
8. Which surgical methods do you use in pediatric stone disease between 0-2 years of age? (you can select more than one option in this question)
9. Which surgical methods do you use in pediatric stone disease between 2-6 years of age? (you can select more than one option in this question)
10. Which surgical methods do you use in pediatric stone disease between the ages of 6-18? (you can select more than one option in this question)
11. Which of the following treatment methods would you prefer for staghorn kidney stones in patients aged 0-2 years?
12. Which of the following treatment methods would you prefer for staghorn kidney stones in patients aged 2-6 years?
13. Which of the following treatment methods would you prefer for staghorn kidney stones in patients aged 6-18 years?
14. Which of the following treatment modalities would you prefer for <10 mm symptomatic pelvic stones in patients aged 0-2 years?
15. Which of the following treatment modalities would you prefer for symptomatic pelvic stones <10 mm in patients aged 2-6 years?
16. Which of the following treatment methods would you prefer for <10 mm symptomatic pelvic stones in patients aged 6-18 years?
17. Which of the following treatment methods would you prefer for symptomatic pelvic stones of 10 - 20 mm in patients aged 0-2 years?
18. Which of the following treatment methods would you prefer for 10 - 20 mm symptomatic pelvic stones in patients aged 2-6 years?
19. Which of the following treatment methods would you prefer for 10 - 20 mm symptomatic pelvic stones in patients aged 6-18 years?
20. Which of the following treatment methods would you prefer for > 20 mm symptomatic pelvic stones in patients aged 0-2 years?
21. Which of the following treatment methods would you prefer for symptomatic pelvic stones > 20 mm in patients aged 2-6 years?
22. Which of the following treatment methods would you prefer for > 20 mm symptomatic pelvic stones in patients aged 6-18 years?
23. Which of the following treatment modalities would you prefer for symptomatic 10-20 mm lower pol calyx stones in patients aged 0-2 years?
24. Which of the following treatment methods would you prefer for 10-20 mm symptomatic lower pol calyx stones in patients aged 2-6 years?
25. Which of the following treatment methods would you prefer for 10-20 mm symptomatic lower pol calyx stones in patients aged 6-18 years?
26. Which of the following treatment modalities would you prefer for symptomatic lower pol calyx stones <10 mm in patients aged 0-2 years?
27. Which of the following treatment modalities would you prefer for symptomatic lower pol calyx stones <10 mm in patients aged 2-6 years?
28. Which of the following treatment modalities would you prefer for symptomatic lower pol calyx stones <10 mm in patients aged 6-18 years?
29. Which of the following treatment modalities would you prefer for symptomatic upper ureter stones in patients aged 0-2 years?
30. Which of the following treatment modalities would you prefer for symptomatic upper ureteral stones in patients aged 2-6 years?
31. Which of the following treatment modalities would you prefer for symptomatic upper ureteral stones in patients aged 6-18 years?
32. Which of the following treatment modalities would you prefer for symptomatic lower ureteral stones in patients aged 0-2 years?
33. Which of the following treatment modalities would you prefer for symptomatic lower ureteral stones in patients aged 2-6 years?
34. Which of the following treatment modalities would you prefer for symptomatic lower ureteral stones in patients aged 6-18 years?
35. Which of the following treatment methods would you prefer for > 2 cm bladder stones in patients aged 0-2 years?
36. Which of the following treatment methods would you prefer for > 2 cm bladder stones in patients aged 2-6 years?
37. Which of the following treatment methods would you prefer for > 2 cm bladder stones in patients aged 6-18 years?
38. Which of the following treatment methods would you prefer for < 2 cm bladder stones in patients aged 0-2 years?
39. Which of the following treatment methods would you prefer for < 2 cm bladder stones in patients aged 2-6 years?
40. Which of the following treatment methods do you prefer for < 2 cm bladder stones in patients aged 6-18 years ?
41. Which of the following do you apply in pediatric stone patients in your daily practice? (you can select more than one option in this question)
42. In your daily practice, which imaging method do you prefer for the first postoperative control in pediatric stone patients?

Figure 1

Preferred diagnostic methods in different age groups



**DG: Direct Radiography, US: Ultrasonography, CT: Computed Tomography*

3. Results

The number of respondents was 95. Of the participants, 11.46% were assistants, 46.96% were specialists, 3.12% were lecturers, 11.46% were assistant professors, 19.79% were associate professors, and 5.21% were professors. A total of 39.58% of the participants worked in university hospitals, 25% in training and research hospitals, 17.71% in state hospitals, and 17.71% in private hospitals. 91.67%, 89.47%, and 80.21% of the participants preferred ultrasonography (US) as the diagnostic method in the 0-2, 2-6, and 6-18 age ranges, respectively. Intravenous pyelography (IVP) was not preferred by any participant **(Fig. 1)**. In response to the question "Which surgical methods do you use in pediatric stone disease?", URS was preferred most frequently between the ages of 0-2 and 2-6 years, followed by mini PCNL; between the ages of 6-18 years, URS was preferred most frequently, followed by RIRS and mini PCNL in equal proportions In treating staghorn kidney stones in the 0-2 and 2-6 age groups, mini PNL was preferred most frequently, followed by standard PCNL. In treating staghorn stones between the ages of 6 and 18, standard PCNL was preferred most frequently, followed by mini PCNL. Surgical treatment of staghorn kidney stones in different age groups was performed independently of both the place of duty and titles ($p > 0.05$) **(Table 2)**.

In all age groups, SWL was the most common procedure for symptomatic pelvic stones smaller than 10 mm, followed by RIRS, which was the second most frequently used. For symptomatic pelvic stones between 10-20 mm in all age groups, mini PCNL was the most commonly used method, followed by RIRS in second place. The most frequently used method for symptomatic pelvic stones larger than 2 cm was mini PCNL in all stone groups. For symptomatic lower pole calyx stones 10-20 mm, mini PCNL was the most frequently used method in all age groups.

Table 2

Preferred treatment methods for staghorn kidney stones in different age groups

Age groups	Treatment Methods	Title						p
		Resident (%)	Specialist (%)	Lecturer (%)	Assistant Professor (%)	Associate Professor (%)	Professor (%)	
0-2	Follow up	9.1	0	0	0	0	0	0.595
	SWL	0	4.3	0	0	0	0	
	Standard PCNL	18.2	8.5	0	20	10.5	20	
	Mini PCNL (<22 F)	54.5	70.2	100	70	78.9	80	
	Micro PCNL	9.1	12.8	0	10	5.3	0	
	Laparoscopic surgery	0	0	0	0	5.3	0	
	Open Surgery	9.1	4.3	0	0	0	0	
2-6	Follow up	9.1	0	0	0	0	0	0.762
	SWL	0	4.3	0	9.1	0	0	
	Standard PCNL	9.1	13	33.3	18.2	11.1	20	
	Mini PCNL (<22 F)	72.7	71.7	33.3	72.7	83.3	80	
	Micro PCNL	9.1	6.5	0	0.	5.6	0	
	Open Surgery	0	4.3	33.4	0	0	0	
6-18	Follow up	9.1	0	0.0	0	0	0	0.168
	Standard PCNL	63.66	53.2	66.7	81.8	31.6	40	
	Mini PCNL (<22 F)	18.2	44.7	33.3	18.2	68.4	60	
	Micro PCNL	9.1	2.1	0	0	0	0	

**SWL: Shock Wave Lithotripsy, PCNL: Percutaneous Nephrolithotomy*

Table 3

Rates of stone surgery according to title

	Age groups	Title						p
		Resident (%)	Specialist (%)	Lecturer (%)	Assistant Professor (%)	Associate Professor (%)	Professor (%)	
Those who perform stone surgery	0-2	27.3	42.6	0	36.4	15.8	0	0.007
	2-6	18.2	31.9	0	36.4	10.5	0	
	6-18	9.1	14.9	0	0	10.5	0	

Table 4

Rates of stone surgery according to place of duty

	Age groups	Place of Duty				p
		University Hospital (%)	Training and Research Hospital (%)	State Hospital (%)	Private Hospital (%)	
Those who perform stone surgery	0-2	23.7	33.3	41.2	35.3	0.364
	2-6	21.1	29.2	29.4	17.6	
	6-18	7.9	8.3	17.6	11.8	

Table 5

Proportions of those who perform metabolic screening and stone analysis and those who do neither, according to the title

	Title						p
	Resident (%)	Specialist (%)	Lecturer (%)	Assistant Professor (%)	Associate Professor (%)	Professor (%)	
Metabolic Screeners	54.5	61.7	66.7	63.6	73.7	60	0.392
Stone Analyzers	90.9	72.3	100	100	84.2	100	0.157
Those Who Do Neither	9.1	19.1	0	0	15.8	0	0.479

For symptomatic lower pole calyx stones smaller than 10 mm, RIRS was the most used method in the 0-2 and 6-18 age groups, whereas SWL was the most frequently used method in the 2-6 age group. URS was the most used method for symptomatic upper and lower ureteral stones in all age groups. For bladder stones larger than 2 cm, endoscopic surgery was the preferred method in the 0-2 and 2-6 age groups, while endoscopic surgery and percutaneous surgery were equally preferred in the 6-18 age group. Endoscopic surgery was the preferred method for bladder stones smaller than 2 cm in all age groups. In different age groups, performing stone surgery was related to title ($p = 0.007$) **(Table 3)** but not to place of duty ($p = 0.364$) **(Table 4)**. In daily practice, 82.29% of the participants recommended stone analysis and 63.54% recommended metabolic screening, while 13.54% did neither. When we looked at the rates of performing stone analysis according to the place of work, 92.1% of those working in university hospitals, 79.2% of those working in training and research hospitals, 52.9% of those working in state hospitals, and 94.1% of those working in the private hospital performed stone analysis ($p = 0.002$). On the other hand, performing metabolic screening and stone analysis did not depend on title ($p = 0.392$, $p = 0.157$, respectively) **(Table 5)**. At the first postoperative visit, 93.75% of the participants preferred US.

4. Discussion

In PSD, the guideline [11] strongly recommends direct radiography (DG) and US as primary for diagnosis and follow-up. In line with the guidelines, urologists preferred US the most. However, contrary to expectations, DG was less frequently preferred. IVP was not chosen, indicating that urologists had abandoned this diagnostic modality. We believe that non-contrast CT should be selected in preoperative patients. We know that CT provides excellent anatomical information and has high specificity. However, some studies [12,13] in the literature recommend CT as the first diagnostic method for PSD because it is the gold standard diagnostic method. Radiation is a major problem for pediatric patients. Therefore, US should be performed first, at least to determine urgent conditions such as hydronephrosis and pyonephrosis. This way, pediatric patients will be protect pediatric patients from unnecessary radiation exposure in non-emergency situations. For children for whom non-contrast CT is planned, it is also strongly recommended in the guideline [11] that CT should be low dose. Urologists should consider this recommendation and prefer low-dose, non-contrast CT in children.

In general, URS is the most commonly used surgical method in PSD because it is easily accessible to most urologists and minimally invasive. EAU guidelines [11] recommend PCNL for kidney stones larger than 2 cm. Participants in the study generally follow the guideline recommendations. In staghorn kidney stones, mini PCNL is performed more frequently in patients aged 0-2 and 2-6 years because the kidney is relatively smaller. Between the ages of 6 and 18, standard PCNL is preferred more frequently as the kidney approaches adult size. In addition, although AUA (American Urology Association) guidelines [10] states that SWL can be performed in pediatric patients for stones larger than 20 mm, a ureteral catheter (Double J) or percutaneous nephrostomy should be placed before the procedure. Since this method requires extra intervention in pediatric patients, it has not been a preferred treatment method. The fact that the surgical treatment of staghorn kidney stones can be performed independently of both the place of duty and title suggests that the experience of urologists in Turkey is similar.

In the literature, stone-free rates ranging from 57% to 97% in

the short term and 57-92% in the long term after SWL are available. [9,14,15] Following the guideline [11] recommendations, symptomatic pelvic stones smaller than 10 mm in diameter are treated with SWL in all age groups, with the endourological methods (RIRS and PCNL) being the second most common treatment modality. We can conclude that urologists who prefer RIRS as the first treatment method may not have the opportunity to perform SWL or may be unable to perform SWL due to contraindications. The fact that SWL requires anesthesia in pediatric patients is a relative disadvantage.

Recent guidelines [11] recommend SWL / PCNL / RIRS as the first choice of surgical treatment for 10-20 mm pelvic stones. SWL is more likely to require more than one session. For this reason, we believe that mini PCNL is the first preferred method among the participants. RIRS was chosen as the second method of choice. The aim is to make patients stone-free with the minimum number of sessions possible.

Although observation or SWL is recommended as the first choice for lower pol stones smaller than 10 mm in the recently published guideline [11] the participants used SWL as the first choice and RIRS as the second choice only for patients between 2 and 6 years of age. In other age groups, RIRS was preferred most frequently. We know that the success of SWL is lower pole stones than for stones in other localizations due to the location. For this reason, the participants may prefer RIRS over SWL.

In previous studies, the stone-free rate with URS ranged between 82% to 100%. [16,17] However, endoscopic surgery via the retrograde route is relatively more complex for upper ureteral stones. Middle and lower ureteral stones can be removed more easily with URS. Participants reported URS as their first choice for symptomatic ureteral calculi in all age groups. However, guideline [11] recommends SWL as the first-line treatment for upper ureteral stones.

There are three different methods for the surgical treatment of bladder stones: endoscopic (transurethral/percutaneous), SWL, and open surgery. Guidelines [11] recommends that endoscopic methods should be preferred primarily. Participants frequently preferred endoscopic methods, following guideline recommendations and in their daily practice.

The statistical difference in stone analysis according to the place of duty is likely due to the inadequacy of facilities in state hospitals. The conditions of state hospitals should be improved. The fact that stone analysis and metabolic screening are independent of the title shows that urologists perform stone analysis when they have sufficient facilities.

US, which is not as effective as computed tomography in stone detection, is preferred as a postoperative control imaging method because it is easily accessible to urologists, does not involve radiation, and provides reliable information about the condition of the collecting system.

5. Conclusion

The management of urinary tract stones in pediatric patients involves a complex set of processes. The sole aim is not just to achieve stone-free management. Since children are in a high-risk group, prevention of recurrence is equally important, along with stone analysis and metabolic evaluation. Urologists in Turkey generally following the guidelines. However, this is not always possible due to a lack of facilities. The necessary facilities for urologists need to be improved.

Statement of ethics

This study was approved by the Ethics Committee of Çukurova University, Medical Faculty, Adana, Turkey (2023-138/63)

Source of Finance

The authors declare that they have received no financial support for this study

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

NA: Conception, Data Collection, Design, MD: Conception, Materials, Analysis, IOY: Analysis, Writing, Design, TA: Data collection, Writing, Critical Review, IAA: Data collection, Supervision, Materials, NS: Critical Review, Literature Review

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Analysis of Temporomandibular Joint Dislocations in a Province of Türkiye

Yenal Karakoç[1], Ömer Kaçmaz[1], Öner Avınca, Mahmut Taş[1]

1 Health Sciences University, Gazi Yasargil Research and Training Hospital, Emergency Department, Diyarbakır, Türkiye

Abstract

Aim: It is extremely important to analyse the etiology of Temporomandibular Joint (TMJ) dislocation, take the correct history, and diagnose the signs and symptoms correctly so that the treatment can be performed as soon as possible without delay. In this study, we aimed analysis of the patient's management and applicability to the emergency department due to temporomandibular joint displacement with the literature.

Methods: In our single-center retrospective study, all patients who applied to the emergency department of our hospital between January 2016 and April 2022 due to mandibular dislocation were initially included in the study.

Results: A total of 67 [n=67] patients who applied to our emergency clinic due to jaw dislocation were recorded. 31 [46.3%] of all patients were evaluated as first-time dislocations and 36 [53.7%] with recurrent dislocations. When we evaluated the jaw dislocations according to the gender of the patients, we observed that the female gender was more affected in both first-time and recurrent dislocation patients. Bilateral dislocations were the most common in patients with first-time jaw dislocation 29 [93.5%]] as well as in patients with recurrent dislocations 34 [94.4%]]. When we evaluated the groups, it was found that traumatic causes 19 [61.3%]] were more common in first-time jaw dislocations, and non-traumatic causes were more common in recurrent dislocations 27 [75%]].

Conclusion: Although emergency physicians rarely encounter TMJ dislocation, they need to know the treatment options and the importance of early reduction to ensure patient comfort and joint function.

***Keywords**: TMJ dislocations, manual reduction, emergency department*

1. Introduction

Temporomandibular joint (TMJ) dislocation; can be defined as bilateral or unilateral displacement of the mandibular condyle from the articular surface of the temporal bone (glenoid fossa).[1]

TMJ dislocation can occur as a result of trauma or without trauma. Yawning may occur because of the patient having a seizure or by the forceful excessive opening of the jaw. However, it can also occur iatrogenically as a result of pressure applied during dental treatments or during medical interventions such as endotracheal intubation, bronchoscopy, and laryngoscopy.[2,3-7]

Determining the risk factors for TMJ dislocation during the evaluation of the patients is important in determining the risk of recurrence that may occur after treatment. Among the risk factors; are previous dislocations, structural or anatomical disorders, connective tissue disorders affecting stability, neurodegenerative or neuro dysfunctional disorders, increasing age, and changes in the patient's tooth structure.[3,4,8,9]

TMJ dislocation has an incidence of approximately 3% of all dislocations in the body. Its annual incidence has been reported as 5.3 in 1,000,000 patients admitted to the emergency department [ED].[10,11] When the literature is examined, the predominance of the female gender is observed and it is thought that this situation may be related to hormonal imbalance.[12]

Anterior dislocations usually develop due to atraumatic causes. It is the most common type of mandibular dislocation. Posterior, lateral, and superior dislocations, which are less common, are usually associated with high-energy trauma. Bilateral TMJ dislocation was observed more frequently than unilateral dislocation.[13] TMJ dislocations; can be defined as acute or recurrent chronic. Chronic dislocations are defined as non-self-limiting and progressive dislocations.[14] Chronic dislocations are dislocations that generally last longer than 3 days. However, there is no definite consensus on this issue. Treatment of chronic recurrent dislocations usually requires open surgery. Acute dislocations: It is usually treated with closed reduction. Before the reduction procedure, sedation and muscle relaxant medication may be required.[15-17]

In the evaluation of the patient with TMJ dislocation at the emergency service application; Stabilizing the airway, respiration, and circulation without wasting time and intervention in life-threatening situations should be a priority.[18] If there is a fracture or chronic dislocation as a result of physical examination and imaging, consul-

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tation with the relevant clinics may be appropriate. Patients with serious injuries may require surgical reduction.[19,20]

On physical examination, there may be tenderness in the pre auricular region and deviation of the chin in the TMJ region. During a physical examination, the mandible should be examined for symmetry to determine whether the dislocation is unilateral or bilateral. It should be noted that bilateral dislocations will cause an open, fixed chin appearance in the midline. Physical examination of superior dislocations usually reveals a protrusion in the pre auricular and temporal regions of the face. It should be kept in mind that the trigeminal nerve [5th cranial nerve], facial nerve [7th cranial nerve], and vestibulocochlear nerve [8th cranial nerve] may be damaged in patients with superior dislocation.[2,21]

A patient with TMJ dislocation in the emergency department may require sedation to reduce pain and anxiety before reduction. Short-acting benzodiazepines [Midazolam] and opioid analgesics such as fentanyl can be used. The use of propofol for procedural sedation is beneficial for TME reduction due to its short half-life and antiemetic effect.[22] Local anesthetic application to create nerve block can also be considered as other options that can be used before reduction. Infiltration of the TMJ capsule with masseter peripheral nerve block and deep temporal nerve can be accomplished by reducing muscle spasm and pain and allowing minimal painful reduction.[23]

History and physical examination are usually sufficient for the diagnosis of TMJ dislocations. Therefore, radiological evaluation may not be necessary. Computed tomography [CT] scanning is the imaging modality of choice in the presence of an uncertain diagnosis or suspected fracture.[24] Imaging is absolutely necessary after reduction, as an iatrogenic fracture may occur following severe manipulation of the mandible during its reduction. For women of childbearing age, a pregnancy test should be performed prior to imaging.[2]

Patients can usually be discharged after successful reduction. After reduction, patients should be fitted with a head-chin bandage or a rigid neck brace to prevent re-dislocation. Patients who have undergone successful reduction should be advised not to open their mouths wide [greater than 2 cm] for 1-3 weeks. In patients who have undergone reduction, care should be taken to support the jaw while yawning.[2,25]

2. Materials and Methods

In our single-center retrospective study, all patients who applied to the emergency department of our hospital between January 2016 and April 2022 due to mandibular dislocation were initially included in the study. The analysis was performed using the S03.0 [Jaw dislocation] code, which is included in the ICD [International statistical classification of diseases and related health problems] coding system from the hospital computerized database. A total of 287,187 patients were admitted to the Emergency Department of our hospital between the dates of the study. Between the specified dates, a total of 139 patient applications due to mandibular dislocation were detected and evaluated. Patients who required open surgery were excluded from the study.

As a result of the evaluation, those who applied with the same name and ID number in different time periods were evaluated as recurrent dislocations, and a total of 67 patients were included in the study.

Descriptive statistical evaluation was performed. The age, gender, presence and number of previous jaw dislocations, the side of the jaw dislocation [right, left and bilateral], the method used in the reduction, the mechanism of the jaw dislocation [traumatic and non-traumatic], and whether drugs were used before reduction were recorded. Continuous variables were analyzed using mean±standard deviation, minimum and maximum values, while categorical data were analyzed using percentages and frequencies values. The association among categorical data was evaluated using the Chi-Square, Fisher's Exact test statistic.

The research protocol was reviewed and approved by Clinical Research Ethics Committee. The study was performed according to the Declaration of Helsinki.

3. Results

A total of (n=67) patients who applied to our emergency clinic due to jaw dislocation between January 2016 and April 2022 were recorded. 31 (46.3%) of all patients were evaluated as first-time dislocations and 36 (53.7%) recurrent dislocations.

The patients were divided into two groups, first dislocation (Group 1) and recurrent dislocation (Group 2). When we evaluated the jaw dislocations according to the gender of the patients, we observed that the female gender was more affected in both first-time and recurrent dislocation patients. When we evaluated the direction of the jaw dislocation, it could not be evaluated because the patients could not show the direction of the dislocation (superior, anterior, posterior or lateral). Since mandibular dislocations were recorded and questioned as right, left and bilateral in our records; Bilateral dislocations were the most common in patients with first-time jaw dislocation 29(93.5%)) as well as in patients with recurrent dislocations 34 (94.4%).

This study was conducted to determine the etiological causes of patients with jaw dislocation as evidenced by radiological evaluation. The cases that occurred as a result of the patients falling while walking, hitting their chin on a vehicle, being beaten by someone else, falling from a bicycle, and those that occurred due to trauma from an epileptic seizure were recorded as traumatic jaw dislocation. Patients with jaw dislocation that occurred spontaneously, i.e. without any identified traumatic event, were categorised as non-traumatic cases.

When we evaluated the groups, it was found that traumatic causes 19(61.3%) were more common in first-time jaw dislocations, and non-traumatic causes were more common in recurrent dislocations 27(75%). When we evaluate the causes of mandibular dislocation according to gender; It was seen that the most common cause in women was yawning 33(67.3%) and the most common cause in men was trauma. Data on first time or recurrent jaw dislocations are shown in **Table 1**, and data on the mechanism of chin dislocation according to the gender of the patients are shown in **Table 2**.

Our hospital provides service to all age groups who apply in the emergency department trauma department. The mean age of our patients in group 1 was 33.84±19.44 years old, mean age in group 2 was 33.94±18.05 years old, the youngest patient was 5 years old, and the oldest patient was 88 years old. The median age of the patients was 27.

Jaw reduction was performed using the Hippocratic method in all patients admitted to the study with mandibular dislocation. Midazolam was administered for sedation in 6 (9%) patients during chin reduction. Medication was not administered to the remaining 61 (91%) patients. After the reduction, the patients were discharged with a Barton bandage.

Table 1

Evaluation of demographic data of patients between groups

		First time dislocation [Group 1) n=31	Recurrent dislocation [Group2) n=36	Total n=69	p
Gender	Female	24(%77.4)	25(%69.4)	49(%73.1)	0.583^{x2}
	Male	7(%22.6)	11(%30.6)	18(%26.9)	
Direction of Jaw Dislocation	Right	2(%6.5)	1(%2.8)	3(%4.5)	0.505^{x2}
	Left	0	1(%2.8)	1(%1.5)	
	Bilateral	29(%93.5)	34(%94.4)	63(%94)	
Presence of trauma	Yes	19(%61.3)	9(%25)	28(%41.8)	0.003^{x2}
	No	12(%37.8)	27(%75)	39(%58.2)	
Cause of Jaw Dislocation	Simple Fall	2(%6.5)	2(%5.6)	4(%6)	0.003^{x2}
	Yawning	12(%37.8)	27(%75)	39(58.2)	
	Trauma	17(%54.8)	5(%13.9)	22(%32.8)	
	Epilepsy	0	2(%5.6)	2(%3)	
Presence of Pre-Reduction Drug Use	Yes	28(%90.3)	33(%91.7)	61(%91)	0.05 ^{x2}
	No	3(%9.7)	3(%8.3)	6(%9)	
Age		33.84±19.44	33.94±18.05	33.90±18.56 Min=5 Max=88	

^{x2} *Pearson Chi-square*

Table 2

Evaluation of the jaw dislocation mechanism according to the gender of the patients

	Female n=49(%73.1)	Male n=18(%26.9)	Total n=67	P
Simple Fall	4(%8.2)	0	4(%6)	0,04 ^{x2}
Yawning	33(%67.3)	6(%33.3)	39(%58.2)	
Trauma	12(%24.5)	10(%55.6)	22(%32.8)	
Epilepsy	0	2(%11.1)	2(%3)	

x2 Pearson Chi-square

4. Discussion

Temporomandibular joint (TMJ) dislocation is a rare condition of the facial skeleton. The incidence rate of TMJ dislocation among whole body dislocations is approximately 3%. The annual incidence rate associated with emergency service admissions was found to be between 25-53/100.000 in studies.[1,2] Our study revealed that TMJ dislocations constitute 48/100,000 of all emergency department trauma admissions. This rate was consistent with the literature.

It is extremely important to analyze the etiology of TMJ dislocation, to take the correct history, and to diagnose the signs and symptoms correctly so that the treatment can be performed as soon as possible without delay.[23] When we evaluated the etiology of TMJ dislocations of our patients, we observed that the most common non-traumatic causes were 39 (58.2%) both in first-time and recurrent dislocations. While trauma was less common in the development of recurrent dislocation with first-time dislocation, non-traumatic causes were more common and were statistically significant (P=0.003)

When we examine the formation mechanism of jaw dislocation according to the gender of the patients; we observed that both first-time and recurrent dislocations were more common in women 49 (73.1%)). Although there are different results in the literature regarding the distribution of TMJ dislocations by gender, it is understood that it is generally more common in women.[14,26]

However, when we look at the distribution of causes of TMJ dislocation by gender, we found that non-traumatic causes (such as yawning) were more common in females 33(67.3%)), while traumatic causes were more common in males 10 (55.6%)). The difference was statistically significant (p=0.04). When we analyzed the etiological cause of TMJ dislocations between the groups, it was found that the most common cause in group 1 with jaw dislocation was due to trauma with 17 (54.8%) in the group with recurrent dislocation. On the other hand, we observed that the most common cause was 27 (75%) non-traumatic stretching, which was statistically significant (p=0.003)

Babatunde O Akinbami stated in a systematic review of 128 articles that the most common etiological cause was trauma with 60%.[27] In a study by Giorgos Papoutsis et al. in Switzerland, they stated that although the etiopathogenesis of spontaneous dislocation is generally unknown, it often occurs in association with yawning and less frequently after mild facial trauma.[14] Prechel et al. an-

other review noted that the most common triggers of TMJ dislocation were daily activities associated with wide opening of the mouth, such as yawning, laughing, or biting.[13]

When we evaluate the direction of the dislocation in the TMJ dislocation; bilateral dislocations were more common in 29 (93.5%) patients in the first-time dislocation group and 34 (94.4%) in the recurrent dislocation group, which is consistent with the literature.[14,26,28]

When we scan the literature; the most commonly used technique for reduction in patients with TMJ dislocation is the Hippocratic reduction method.[13,27,29,30] In our study, all our patients were reduced by an emergency medicine specialist in the emergency room. All patients were reduced by the Hippocratic method. During the reduction, midazolam was given to 6 patients in total, 3 in each group, for sedation. When we look at the literature, we observed that the frequency of sedation and analgesia use is not high.[14,28] After the reduction, all patients were discharged with the Barton Bandage applied. Since the patients did not come to the emergency room for control after they were sent, long-term follow-up could not be done. It has been observed in the literature that there is no standard treatment method for TMJ dislocation, but early reduction is the most effective way.[28]

4.1. Limitations

The single-center retrospective nature of our study can be considered as a limitation. The fact that the pain levels of the patients were not questioned, the anatomical aspect of the joint dislocation could not be shown by the patients (anterior, posterior, superior or lateral), and the comparison of manual reduction methods can be considered as limitations. Since it is recommended that patients go to the relevant specialty for follow-up after treatment in the emergency department, the lack of long-term follow-up can also be considered as a limitation.

5. Conclusion

Although emergency physicians rarely encounter TMJ dislocations, they need to be familiar with TMJ dislocations and treatment options to ensure patient comfort and joint function. It is also supported by the literature that early reduction is effective as soon as possible. For this reason, it is thought that medical history and physical examination are essential in TMJ dislocations, and that early manual reduction will be successful after physicians receive adequate training. It should not be forgotten that patients with recurrent TMJ dislocations who apply to the emergency department should be referred to the relevant clinics for treatment after reduction.

In addition, the low need for sedation-analgesia and imaging, high reduction success, when performed with the appropriate technique, support that reduction applications can also be performed in primary health care institutions.

Statement of ethics

This study was approved by the Ethics Committee of Gazi Yaşargil Training and Research Hospital, University of Health Sciences (date: 07.04.2022 number: 61). The study was performed according to the Declaration of Helsinki.

Source of Finance

The authors declare that they have received no financial support for this study

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The authors declare that they have no conflict of interest.

Availability of data and materials

The data supporting the conclusion of this article will be available by the authors without undue reservation.

Author contributions

All authors contributed to the article.

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Patient Blood Management in Pediatric Cardiac Surgery

Feride Karacer[1]

1 Department of Anesthesiology and Reanimation, Cukurova University Faculty of Medicine, Adana, Türkiye

Abstract
Children undergoing open heart surgery are often exposed to allogeneic blood products due to developmental changes in their hemostatic system and inflammation, use of anticoagulants, hemodilution and coagulopathy due to CPB. The complexity of surgical procedures, complex cardiopulmonary interactions and the risk of inadequate oxygen delivery and postoperative bleeding increase the use of blood products. Patient blood management aimed at minimizing blood product transfusion is associated with improved patient outcomes. Safe conservative blood management practices covering the pre-, intra- and postoperative periods result in reduced blood product transfusion. This review summarizes the current evidence on anemia management and blood transfusion practices in the perioperative care of children undergoing cardiac surgery.
Keywords: *Pediatrics, patient's blood management, cardiopulmonary bypass*

1. Introduction

Pediatric cardiac surgery is associated with a significant risk of bleeding and often requires allogeneic blood transfusion. Anemia and coagulopathy are observed perioperatively in neonates and children undergoing cardiac surgery due to complex congenital heart disease and prolonged cardiopulmonary bypass (CPB)[1]. Corrected gestational age, weight, degree of cyanosis and/or intracardiac mixing, immaturity of the hemostatic system, degree of hemodilution, hemostatic alterations and activation of the coagulation system induced by CPB are central features in the management of bleeding and coagulopathy in this special group of patients. Excessive blood loss and consumption of blood products are inevitable in patients with complex congenital heart disease. However, anatomical and physiological variations in children and differences in surgical approaches, CPB techniques and perioperative management between centers make it difficult to generalize patient blood management[2-4]. Studies in children undergoing cardiac surgery are mainly observational and the results do not provide high quality evidence.

Allogeneic blood transfusion can be a life-saving intervention for neonates and children with massive hemorrhage or severe anemia. However, transfusion of blood products is associated with pulmonary complications, thrombosis, transfusion-associated circulatory overload, allergic reactions, prolonged mechanical ventilation, prolonged ICU and hospital stay, infectious risks and mortality[5-7]. Children are also at higher risk of transfusion-related complications than adults[8]. Therefore, minimizing transfusion may be beneficial in pediatric cardiac surgery patients.

Patient blood management strategies aim to optimize the care of patients who require transfusion. Efforts to correct preoperative anemia and coagulopathy, improve homeostasis, reduce bleeding, limit blood collection and incorporate blood-sparing techniques are important points of PBM[9,10]. Pediatric patients are exposed to potential complications associated with red blood cell (RBC) transfusion because of the higher transfusion threshold for children than adults. PBM proposes the restrictive transfusion approach and should be applied to the pediatric cardiac surgical population[11]. Pediatric patients are exposed to potential complications associated with red blood cell (RBC) transfusion because the transfusion threshold is higher in children than in adults. PBM proposes the restrictive transfusion approach and should be applied to the pediatric cardiac surgical population[11].

This review aims to present the current literature on PBM in children with CHD undergoing open heart surgery.

Preoperative Patient Blood Management

Preoperative assessment includes evaluation of patient risk factors, surgical approach, staffing and equipment requirements and should be discussed by a multidisciplinary care team (cardiac surgery, anesthesia, cardiology and intensive care)[12]. The involvement of perfusionists and transfusion center staff in the management of these patients is essential for successful PBM[13]. In order to assess the risk of coagulopathy and intraoperative bleeding, a detailed history should be taken, inquiring about medications and supplements taken, relevant medical history, previous surgery and family history. Laboratory tests for anemia and coagulation parameters should be performed and abnormal results should be treated preoperatively in elective cases[13].

One of the pillars of PBM programs is the diagnosis and treatment of preoperative anemia. Children with CHD range from neonates to adolescents with cyanotic or non-cyanotic heart defects resulting in variable baseline hemoglobin (Hb) and ferritin levels. The

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optimal preoperative Hb concentration for these children is uncertain, especially in patients younger than 6 months or with chronic cyanosis[14].

Iron deficiency (ID) is the most common nutritional deficiency in children and has been defined as a comorbidity in children with chronic conditions such as CHD, heart failure, chronic inflammation, hematological disorders[15]. In addition, ID is a known risk factor for perioperative blood transfusion in the pediatric surgical population[16]. Gao et al.[17] investigated preoperative ID and its association with clinical outcomes in 314 children undergoing cardiac surgery with CPB. They reported that ID was associated with preoperative anemia and cyanotic heart disease and was an independent risk factor for postoperative blood transfusion.

As preoperative anemia and perioperative blood transfusion are associated with poor postoperative outcomes in neonates and pediatric noncardiac and cardiac surgical patients, correction of ID and anemia may reduce perioperative transfusion and is recommended in several guidelines[18-21]. However, this association may be difficult to detect in cyanotic children, who may have ID anemia even with elevated hemoglobin levels.

Preoperative iron supplementation has been studied in adult patients undergoing cardiac surgery in many trials[20,22]. In these studies, hemoglobin levels increased significantly and blood transfusions decreased perioperatively. However, such studies in pediatric cardiac patients are scarce. Otsuka et al.[15] administered oral iron supplementation to children with CHD for 3-12 weeks preoperatively and found that preoperative hemoglobin levels were significantly higher in children treated with iron. Although oral iron treatment has advantages such as low cost, ease of access and relative safety, a treatment period of 2-4 weeks is required to increase hemoglobin levels. The choice of oral or intravenous (IV) iron therapy should therefore be based on patient preference, degree of anemia and timing of surgery. Newer IV iron preparations such as ferumoxytol and ferric iron gluconate are reliable options for rapid iron replacement[23]. Hassan et al.[23] administered IV iron (ferumoxytol) to 54 children with ID anemia and demonstrated that ferumoxytol was effective in the treatment of IDA. In addition, the slow infusion rate and close monitoring allowed early detection of the rare adverse drug reactions.

The use of erythropoiesis-stimulating agents such as erythropoietin in the preoperative period in adult and pediatric patients is limited and poorly studied. Ootaki et al.[24] administered recombinant human erythropoietin subcutaneously to 82 children (72 with noncyanotic heart disease and 10 with cyanotic heart disease) 7 days before surgery. They reported that a single dose of erythropoietin without autologous blood donation increased hemoglobin levels. The Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) guidelines recommend diagnosis and treatment of preoperative iron deficiency anemia with oral or intravenous iron (Grade 1C) and suggest consideration of preoperative erythropoietin (Grade 2C) in pediatric cardiac surgery patients[25].

Intraoperative Patient Blood Management

Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) is a blood conservation strategy in which one or more units of the patient's own whole blood are replaced with an equal volume of crystalloid or colloid fluid before surgery and reinfused at the end of surgery. The collected blood contains clotting factors, red blood cells and platelets and is not subject to the harmful effects of the CPB machine. Intraoperative bleeding is diluted and the reinfusion of collected blood reduces the amount of blood lost at the end of surgery as a source of clotting factors and platelets[26].

The use of ANH in the pediatric surgical population is limited. However, in major pediatric surgery, great care must be taken to maintain normovolemia, as hypovolemia due to blood loss is the most recognized cause of anesthesia-related cardiac arrest in pediatric patients[27]. Sebastian et al.[28] studied ANH in 50 pediatric patients undergoing cardiac surgery with CPB and demonstrated that ANH protected platelets from the deleterious effects of CPB and improved hemostasis with autologous whole blood at the end of surgery. However, higher ANH volumes (ml/kg) and longer storage times increased the need for intraoperative transfusion. In a small study of 12 pediatric cardiac surgery patients, ANH was safe as a strategy to reduce blood component therapy; however, the study failed to demonstrate a reduction in perioperative transfusion or improvement in postoperative outcomes[29]. Overall, there is no clear recommendation that ANH is effective in children undergoing cardiac surgery with CPB due to conflicting results. The NATA guideline recommends against the use of routine ANH in children undergoing cardiac surgery with CPB (Grade 1C)[25].

Cell Salvage

Intraoperative cell salvage (ICS) is another method of reducing allogeneic red blood cell (RBC) transfusion. It recovers and purifies blood lost in the surgical field and returns the resulting red blood cell concentrate to the patient[30]. Due to the minimal blood volume required for the washing process in cell salvage, this method has limited use in infants and young children during pediatric cardiac surgery[31]. However, new cell salvage devices with small volume centrifugal beakers allow blood salvage even in neonates and small infants. Golab et al.[32] demonstrated that the use of a cell saver significantly reduced postoperative allogeneic blood transfusion in infants undergoing CPB surgery with a body weight of less than 10 kg. In addition, erythrocyte washing may reduce inflammatory biomarkers and systemic inflammation[33]. The NATA guideline recommends the use of cell salvage in pediatric cardiac surgery to reduce perioperative transfusion (grade 1C) and suggests active salvage of residual blood from the CPB circuit (grade 2C)[25].

Antifibrinolytic Agents

Antifibrinolytic agents such as tranexamic acid (TXA) or ε-aminocaproic acid (EACA) competitively inhibit the conversion of plasminogen to plasmin and reduce fibrin degradation. Activation of fibrinolysis is a major cause of bleeding in open heart surgery and antifibrinolytic agents significantly reduce blood loss and transfusion[34]. A meta-analysis of 30 trials (aprotinin n = 14, TXA n = 12 and EACA n = 2) reported that all agents reduced mean 24-hour blood loss and blood product transfusion[34]. Therefore, the agent with the best safety profile should be used, but sufficient data are lacking.

Intraoperative TXA dosing regimens used in different centers are quite variable due to various concerns regarding pharmacokinetic mechanisms and adverse effects. Some centers have used 3 boluses of 10 to 100 mg/kg, while others have used a loading dose of 10 to 100 mg/kg followed by continuous infusion[35]. To maximize the antifibrinolytic effect of TXA and avoid dose-related side effects, including seizures, it is important to use the lowest effective dose possible. Recent studies in children undergoing cardiac surgery have suggested the following dosing regimen: intravenous loading dose of 30 mg/kg (age <12 months) or 10 mg/kg (age ≥12 months); followed by infusion of 10 mg/kg/hr[36]. Therefore, large comparative studies are needed to investigate the relative safety and appropriate dosing regimens in children.

The NATA guideline recommends prophylactic administration of lysine analogues (either TXA or EACA) to all neonates and children undergoing surgery with CPB to reduce perioperative bleeding

and transfusion (Grade 1B) and discourages the administration of high doses of lysine analogues (either TXA or EACA) because of the risk of clinical seizures (Grade 1C)[25].

Coagulation Assessment

Systemic anticoagulation is provided by unfractionated heparin (UFH) during CPB. UFH inhibits thrombin, Factor Xa and activated intrinsic coagulation factors via antithrombin[37]. Monitoring of ACT, heparin concentration (anti-Factor Xa [aFXa] activity) or whole blood heparin concentrations can be used to adjust UFH dosing[38]. ACT and automated protamine titration devices are generally preferred for rapid point-of-care assessment. 400 U/kg heparin is effective in prolonging the activated clotting time (ACT) >480 seconds in infants and children[37]. However, due to low antithrombin levels in neonates and infants, weight-based doses have been shown to inadequately suppress thrombin generation[39]. In addition, differences in anticoagulant efficacy have been reported between different commercial heparins[40]. If heparin resistance is present and antithrombin deficiency is excluded, an additional 100 U/kg is recommended. In the presence of heparin resistance secondary to antithrombin deficiency, fresh frozen plasma (10 mL/kg) or antithrombin supplementation is recommended[25].

Protamine is used to neutralize heparin after CPB and the dose of protamine is usually administered as a 1:1 ratio of protamine to heparin. However, a 1:1 ratio may lead to protamine overdose and bleeding. The use of a protamine-heparin ratio of 1:1 or higher is not recommended as excess protamine may increase the risk of bleeding[25]. Thus, age-related differences and heparin-protamine interactions complicate heparin dosing and protamine reversal in pediatric cardiac patients[41].

Bivalirudin, a direct thrombin inhibitor, is the anticoagulant of choice when heparin is contraindicated or must be avoided. The recommended dose to maintain an ACT of more than 480 seconds was 1 to 2 mg/kg followed by a 2 to 3 mg/kg/h infusion[42].

Cardiopulmonary Bypass

Hemodilution and Target Hemoglobin

Patient size and bypass circuit volume ratio determine the degree of hemodilution during CPB. In infants weighing less than 8 kg, severe hemodilution occurs, causing fluid shifts and reducing platelets and coagulation factors[43]. Therefore, the bypass circuit in pediatric patients is generally primed with blood to maintain a predefined Hct[44].

Total priming volume is directly related to the amount of perioperative transfusion, and lower priming volumes are associated with lower transfusion volumes during CPB[45]. In addition, lower priming volume leads to improved water balance and reduced need for postoperative mechanical ventilation[46]. Consequently, miniaturization of the circuit and use of ultrafiltration, hemoconcentrator and cell saver can reduce hemodilution and the need for blood product transfusion and improve clinical outcomes[47].

Jonas et al.[48] administered 2 different target hematocrit (Htc) values (20% vs 30%) to infants < 9 months. The lower Htc group (20%) had a lower cardiac index, higher post-CPB lactate levels and increased total body water on postoperative day 1. Although there was no difference in the amount of blood product transfusion and adverse events between the 2 groups, the low Hct group had significantly worse psychomotor development scores at 1 year. In another study, Newburger et al.[49] compared target Hct values of 25% vs 35% during hypothermic CPB in infants. The 25% group had a more positive fluid balance but similar blood product transfusions, adverse events and developmental outcomes. As a result of these studies, a target Hct value of >25% during CPB is recommended for optimal neurodevelopmental outcome.

Priming Fluid

Since the 1990s, physiological salt solutions (commonly Plasmalyte) or lactated Ringer's (LR) have been used as the crystalloid priming solution in pediatric cardiac surgery[50,51]. Albumin is often added to the priming solution because of the inability of crystalloid solutions to provide oncotic pressure and reduce the inflammatory response[52]. In a study of 105 children under the age of 3 years, patients were randomized into 3 groups[53]. One group received 10 mL/kg albumin in the priming solution, the second group received 20 mL/kg synthetic colloid in the priming solution and the third group received LR priming solution. The albumin group had significantly higher postoperative platelet counts and plasma colloid oncotic pressures, and significantly less postoperative blood loss and blood product requirements than the other groups. According to the results of this study, albumin may have some advantages in terms of postoperative blood parameters.

The decision to add RBCs to the prime solution depends on the patient's body weight, pre-operative hematocrit, prime volume and acceptable hematocrit after dilution on CPB[54]. Asanginous prime is generally used in infants weighing more than 5-6 kg[55]. Whole blood, erythrocytes or erythrocytes plus FFP can be added to the blood-based prime volume[56]. Fresh whole blood (FWB) has historically been used in pediatric cardiac surgery to stabilize and correct coagulopathy and reduce inflammation. However, FWB is difficult to obtain and test in a timely manner, limiting its use. In pediatric patients younger than 2 years undergoing complex cardiac surgery, the use of FWB has been shown to reduce blood loss[57]. Mou et al.[58] compared FWB with RBC plus FFP for CPB priming in children undergoing cardiac surgery. They found that FWB in CPB priming reduced ICU length of stay and fluid overload.

FFP is often used in CPB priming as a source of fibrinogen and clotting factor[59]. In a study of children aged 1 to 16 years with congenital heart disease, 20% albumin or FFP was used in the CPB prime[60]. Immediately after heparin reversal, hemostatic test results improved in the FFP group, but these results were not maintained 24 hours after CPB. There were no other clinical differences between the groups. In a study of neonates with CHD, Bianchi et al.[61] compared FFP in the prime volume with 5% albumin with erythrocytes in the prime volume. They found that postoperative bleeding was reduced and fibrinogen levels improved in the FFP group. Another study in acyanotic infants under 10 kg compared a 5% FFP priming solution with an albumin priming solution. The FFP priming solution group received more perioperative blood transfusions than the albumin group, but total blood product consumption did not differ between the two groups[62]. The content of the priming solution is usually surgeon and institution dependent, but further study is needed in pediatric cardiac surgery.

The addition of FFP to the prime solution has been suggested in neonates (<30 days) undergoing cardiac surgery (grade 2C). There is no evidence in infants and children undergoing cardiac surgery (C). NATA Colloids (e.g. albumin) should be preferred to crystalloids for clear priming in children undergoing cardiac surgery (Grade 1C).[25]

Ultrafiltration

Ultrafiltration in pediatric cardiac surgery is used to concentrate erythrocytes and coagulation factors and reduce inflammatory mediators by removing excess fluid[63]. Conventional ultrafiltration (CUF) techniques (continuous ultrafiltration and zero balance ultrafiltration) remove fluid from the circulation during CPB and reverse hemodilution[64]. Modified ultrafiltration (MUF) is administered im-

mediately after cessation of CPB, provides maximal hemoconcentration and reduces early postoperative blood transfusion[65]. MUF has been shown to improve pulmonary compliance and gas exchange, increase hematocrit and blood pressure levels. However, Kuranti et al. reported in a meta-analysis that CUF and MUF were safe and effective hemoconcentrators and there was no difference in clinical outcomes[66].

The authors recommend conventional ultrafiltration or ≥10 minutes of modified ultrafiltration for neonates and infants undergoing cardiac surgery with CPB (Grade 1B)[25].

Intraoperative Monitoring of Hemostasis

From birth to adulthood, the concentration of coagulation factors increases while the hepatic synthesis of natural anticoagulants decreases, a phenomenon termed developmental hemostasis[67,68]. Perioperative bleeding and coagulopathy are the major causes of morbidity and mortality in neonates and children undergoing cardiac surgery. Cyanotic heart disease may increase the risk of bleeding by altering the preoperative coagulation profile. In the intraoperative period, major surgery and CPB induce an inflammatory response and coagulopathy. In addition, prime solution causes hemodilution[69]. Blood transfusions are often necessary, but may also be a risk factor for acute lung injury, prolonged extubation time, and prolonged ICU and hospital stay[3,4]. Therefore, clinicians should be prepared to manage blood loss and coagulopathy in pediatric cardiac surgery. Appropriate and timely use of blood products and hemostatic agents according to hemodynamic parameters, laboratory and coagulation tests is one of the key points of patient blood management.

Conventional coagulation tests (aPTT, PT, fibrinogen) are used to diagnose factor deficiencies and the normalized ratio (INR) is used as a guide for vitamin K antagonists in both adults and children[70]. However, as patients are uncoagulable during CPB, these tests cannot be used[25]. In addition, it takes 30-45 minutes to obtain results and the limited information provided does not include platelet count and function and fibrinolysis.

Viscoelastic tests (thromboelastography (TEG) and ROTEM) provide real-time global coagulation status and aid in the management of blood product transfusion in the setting of acute hemorrhage[71]. Viscoelastic assays measure clot initiation, strength and stability by providing a rapid assessment of coagulopathy and have been widely used in adult patients undergoing cardiac surgery[72]. Nakayama et al conducted a study in children undergoing cardiac surgery and found that ROTEM-guided early hemostatic management reduced blood loss, erythrocyte transfusion requirements and ICU length of stay[73]. However, a meta-analysis of 47 articles reported that there is insufficient data in the literature to establish viscoelastic testing as a "gold standard" for the management of bleeding and coagulopathy in pediatric cardiac surgery[74]. In addition, similar to conventional coagulation screening, viscoelastic tests cannot predict bleeding preoperatively in children undergoing cardiac surgery[25].

In the presence of excessive bleeding, the use of intraoperative hemostasis monitoring is recommended (Grade 1B). Viscoelastic tests may be an alternative to standard coagulation tests for intraoperative bleeding management (Grade 2C)[25].

Postoperative Red Blood Cell Transfusion and Thresholds

A prospective multicentre study reported that 79% of pediatric cardiac surgery patients received at least 1 RBC transfusion postoperatively[75]. The amount of RBC transfusion in these patients could not be determined based on intraoperative blood loss or preoperative hematocrit alone[76]. Children under 1 year of age, low birth weight, complex and/or cyanotic congenital heart disease, CPB and preoperative anemia are independent risk factors for RBC transfusion[77]. Although previous studies have shown that RBC transfusion after pediatric cardiac surgery is associated with increased morbidity and prolonged hospital stay, optimal transfusion thresholds have not been defined in these patients. The TRIPICU (The Transfusion Requirements in the Pediatric Intensive Care Unit) study, which investigated transfusion requirements in the pediatric intensive care unit, reported that Hb: 7 mg/dl was tolerated by children without adverse effects[78-80]. In the subgroup analysis, there was no difference in the incidence of multisystem organ dysfunction between children who received a restrictive transfusion strategy (Hb: 7 mg/dl) and a liberal transfusion strategy (Hb: 9.5 mg/dl) in postoperative cardiac surgery patients[81]. However, randomized controlled trials reported that pediatric patients with 20% hematocrit during CPB had a lower postoperative cardiac index, higher lactate levels and poorer neurological outcomes than those with 30% hematocrit[82]. Recent studies suggest that 24% hematocrit may be sufficient in terms of clinical outcomes and neurological outcome[81]. However, higher hematocrits may be required in neonates, cyanotic patients and those with complex cardiac anomalies. Therefore, goal-directed transfusion therapy aimed at a physiological target may be associated with improved clinical outcomes[83]. NATA recommends a postoperative hemoglobin threshold for transfusion in stable, acyanotic cardiac infants of Hb 70 g/L or 80 g/L in the presence of clinical signs suggesting symptomatic anemia (Grade 1B). This threshold is recommended to be 90 g/L in stable, cyanotic cardiac infants with clinical signs suggestive of symptomatic anemia (Grade 1C)[25].

Platelet Transfusion

Thrombocytopenia and platelet dysfunction are consequences of CPB and are associated with postcardiotomy bleeding in neonates and infants[84]. In addition, cyanotic cardiac patients with a hematocrit >50% usually have preoperative thrombocytopenia[85]. Platelet count and function at the end of CPB depend on the duration of CPB, hemodilution and hypothermia[86,87]. The threshold and/or volume of platelet transfusion in pediatric cardiac surgery has not been evaluated in any study and recommendations for platelet transfusion are mainly based on consensus. Group-matched platelet transfusion of 10-20 ml/kg may be given as a first step to restore hemostatic function in the setting of clinical bleeding and/or thrombocytopenia. Clinical assessment, platelet count and VET parameters are helpful in guiding platelet transfusions[11].

Fibrinogen

Decreased plasma fibrinogen has been associated with postoperative bleeding in pediatric cardiac surgery[88]. Fibrinogen can be replenished by administration of cryoprecipitate or fibrinogen concentrate. In bleeding neonates and children, hypofibrinogenemia diagnosed by the Clauss method (<1.5 g/L) or viscoelastic test (class 1C) should be treated with cryoprecipitate or fibrinogen concentrate (class 2C). FFP should be considered ONLY when cryoprecipitate or fibrinogen concentrate is not available (Class 2C)[25].

2. Conclusion

In pediatric cardiac surgery, blood conservation methods including the use of low priming volume circuits, ultrafiltration, microsampling of blood, antifibrinolytics, point-of-care testing and cell salvage blood reinfusion are recommended to reduce blood product consumption. These methods both reduce blood product transfusion and improve clinical outcomes. Patient blood management aims to transfuse the right product, in the right dose, to the right patient, at the right time, for the right reason. A comprehensive and multidisciplinary patient blood management Programme optimizes

patient care, avoids unnecessary blood product transfusions and limits side effects.

Statement of ethics

The author declares that this article does not require ethics committee approval

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Early and Mid-Term Results of Two Stage Revision Arthroplasty in Infected Total Knee Arthroplasty Cases

Abdurrahman Örtücü[1], Edip Bayrak[2], Dilek Yılmaz[2], Seda Zor Çakilli[2], Okay Bulut[3]

1 Nevşehir State Hospital, Department of Orthopedics and Traumatology, Nevşehir, Türkiye
2 Yozgat City Hospital, Department of Infectious Diseases and Clinical Microbiology, Yozgat, Türkiye
3 Medicana Sivas Hospital, Department of Orthopedics and Traumatology, Sivas, Türkiye

Abstract

Aim: Total knee arthroplasty is a treatment method to relieve pain and limitation of movement caused by many knee diseases such as degenerative arthritis. Our aim was to retrospectively evaluate the early and mid-term results of patients with infected total knee arthroplasty who underwent two-stage revision as a treatment method and to compare them with the literature.

Methods: Patients who were diagnosed with infected knee prosthesis in the Orthopedics and Traumatology clinic of our hospital between January 2004 and 2014 and decided to undergo two-stage revision as a treatment method were included in this study. Laboratory results, radiographs, American Knee Society clinical and functional scores were evaluated.

Results: Twenty knees of 19 patients were included in the study. The first stage of two-stage revision was performed in all patients and the second stage was performed in 17 patients. Of the 20 knees diagnosed with infected total knee arthroplasty, 3 had early, 6 had delayed, and 11 had late infection. Preoperative clinical score was 53.29 ± 9.51, postoperative 83.21 ± 9.51 ($p<0.001$); functional score was 40.88 (SD 20.48) preoperatively and 63.23 ± 30.81 ($p=0.018$) postoperatively. The mean degree of flexion was 68.52° ±19.34 preoperatively and 92.64° ±16.30 after revision ($p<0.001$). Compared to the pre-revision period, pain levels of all our patients decreased and walking distances increased

Conclusion: Two-stage revision surgery in infected total knee prostheses was found to be compatible with the literature in terms of eradication of infection, postoperative clinical and functional scores.

***Keywords**: Knee arthroplasty, knee prostheses, prosthetic joint infection*

1. Introduction

As a result of the increase in the number of prosthesis operations performed to reduce the pain caused by joint damage and to increase the reduced range of motion, the number of cases requiring revision is also increasing. The reasons for revision can be divided into two categories as septic and aseptic. In many centers, infection rates are 0.5%-1% after hip replacement and 1%-2% after knee replacement[1]. In a study conducted by Koh et al., the reoperation rate due to periprosthetic infection after total knee arthroplasty was reported as 2%, and half of these infections were reported to be observed in the first 2 years after primary arthroplasty[2]. Similarly, in other studies investigating periprosthetic joint infection, the infection rate after total knee arthroplasty is observed to be between 2% and 5%[3-5]. It is stated that increased body mass index, steroid therapy, diabetes, hypertension and rheumatoid arthritis cause predisposition to prosthesis infections in these patients[6]. There are treatment methods such as antibiotic suppression, flushing-debridement, resection arthroplasty, arthrodesis, one-stage or two-stage revision for patients with infected knee prosthesis. Although there has recently been a tendency towards single-stage revision, the two-stage revision method described by Insall et al. in 1983 is used in delayed, biofilm-formed periprosthetic joint infections. Today, two-stage revision is known to be the gold standard treatment[7-8]. This study aims to evaluate the early and mid-term outcomes of two-stage revision arthroplasty for infected total knee arthroplasty cases. Given the complexity of managing prosthetic joint infections and the limitations of alternative approaches, understanding the effectiveness of two-stage revision during these critical periods can provide valuable insights for

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clinical decision-making. By comparing our findings with existing literature, this study seeks to contribute to the ongoing optimization of treatment protocols for infected TKAs.

2. Materials and Methods

Patients who were diagnosed with infected knee prosthesis in the Orthopedics and Traumatology Clinic of Cumhuriyet University Faculty of Medicine between January 2004 and January 2014 and decided to undergo two-stage revision as the treatment method were selected as the study group. The diagnosis of total knee prosthesis infection was made based on the findings of pain, redness, increased temperature, presence of fistula mouth in the affected knee, findings of implant failure in 2-way direct radiographs, erythrocyte sedimentation rate above 30 mm/m and C reactive protein value above 20 mg/l, and findings of leukocytes and microorganisms in the aspiration material from the joint. The diagnosis was also supported by Technetium 99 scintigraphy. In addition, tissue cultures were taken from at least 3 regions during surgery and evaluated.

Patients included in the study were diagnosed with infected TKA based on clinical symptoms (e.g., redness, pain, or fistula), elevated inflammatory markers (ESR >30 mm/hour, CRP >20 mg/L), and microbiological or imaging findings consistent with infection. Exclusion criteria included insufficient follow-up duration (<6 months), incomplete records, or systemic conditions contraindicating surgery. The follow-up period of the selected patient with the shortest follow-up period was 6 months and it was aimed to give early and mid-term results. For this purpose, the files of the patients eligible for the study were retrospectively analyzed. Patients were contacted again and their last clinical status, laboratory results, radiographs and knee score questionnaires were renewed. Revision knee arthroplasty was performed in the second stage surgery in 18 of 20 knees in which spacers were applied. Then, appropriate antibiotic treatment was applied under the supervision of an infectious disease specialist according to the clinical characteristics of the patients and the microorganism. The duration of antibiotic treatment was decided according to clinical and laboratory results and continued. When infection recurred in one of these patients, arthrodesis was performed because the infection could not be eradicated despite one arthroscopic and two arthrotomic washing debridement and antibiotic spacer placement. The knees of two patients underwent a second washout debridement and antibiotic spacer placement due to intraoperative findings in favor of infection.

Although the infections of these two patients were eradicated during follow-up, revision operation could not be performed. All patients included in the study were contacted by telephone and were asked to come for follow-up. Except for the two patients who died due to other reasons during the follow-up period, all other patients were contacted again. Laboratory results, radiographs, American Knee Society clinical and functional scores were re-evaluated. These two patients who were exited were included in the study because their follow-up data for at least 12 months after the revision operation were available in their files. Pain, redness, increased temperature, presence of fistula mouth in the affected knee, findings of loosening in 2-way direct radiographs, findings of complete blood count, erythrocyte sedimentation value above 30 mm/L, C reactive protein value above 20 mg/L, and also Gram stain and culture-antibiogram from aspiration material from the joint were used to diagnose total knee prosthesis infection. Diagnosis was also supported by Technetium 99 scintigraphy. In addition, tissue cultures were taken from at least 3 regions during surgery and evaluated. The American Knee Society's knee clinical and functional score questionnaire was completed in all patients. Additional problems such as urinary tract infection and deep vein thrombosis were solved. Chronic problems such as diabetes mellitus and hypertension were controlled. Antibiotic therapy was initiated postoperatively based on intraoperative culture results and included agents such as cefazolin or vancomycin. In cases where cultures yielded no growth, empirical antibiotics targeting common pathogens (e.g., Staphylococcus aureus) were administered for 6 weeks. Low molecular weight heparin 0.4 cc once a day were started postoperatively. Haemovac drains were discontinued on the second postoperative day and wound dressings were continued every other day. After the drains were removed, patients were tried to be mobilized with double crutches as much as they could tolerate without loading the operated extremity. When the culture results of the materials taken during the operation were obtained, the patients were consulted to the Department of Infectious Diseases and antibiotherapy was organized according to their recommendations. Patients were called for 3rd and 6th week follow-up. Clinical status of the knee, ESR, CRP, and WBC results were evaluated at the controls. At the end of the 6th week, revision surgery was decided with the approval of the infectious diseases department for patients with regressed infection parameters and clinically resolved infection. If the laboratory results were not good, antibiotic treatment was continued. All patients who were decided for the second stage were prepared for surgery as in the first stage. The previously placed antibiotic spacer was removed. Any dead tissues inside or outside the joint were debrided and samples were taken for culture. In cases of doubt, intraoperative tissue samples were taken and gram staining was performed. If the result supported infection, the antibiotic spacer was reinserted and the protocol in the first stage was followed. If infection was not considered, revision knee prosthesis was placed with antibiotic cement. When intraoperative culture results were obtained, the infectious diseases department was consulted and antibiotherapy was arranged. Discharged patients were called for outpatient follow-up six weeks later. Two-way knee radiographs, ESR, CRP, WBC results were evaluated for loosening. Subsequent follow-ups were performed at one and a half months, third months, four and a half months, sixth months, ninth months, twelfth months and every six months thereafter.

Knee clinical and functional scores of all patients were evaluated preoperatively and postoperatively according to the American Knee Society questionnaire. In this questionnaire, the clinical score is the score value obtained by subtracting the negative scores of flexion contracture, hyperextension and alignment from the positive scores consisting of the degree of pain described subjectively by the patients, range of motion and stability of the joint in all directions. Functional score is the score obtained by subtracting the negative scores given according to the support used by the patient while walking from the positive scores brought by the success in walking and climbing stairs.

The statistical evaluation of the data obtained was done in a computer environment. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (14.0) software. In the analysis, descriptive statistical measures such as mean, median, standard error, minimum and maximum, as well as the significance of the difference between the two pairs was calculated in the comparison of the preoperative and postoperative data of the patients and the data during the period when they were called for control. The homogeneity of the variances was checked with the Levene test. The conformity of the numerical data to normal distribution was evaluated with the Shapiro-Wilk test. For variables showing normal distribution, independent two sample t-test, dependent sample t-test. In the study, $p<0.05$ was considered statistically significant.

The research was conducted in accordance with the 1975 Helsinki Declaration. Approval was obtained from the Cumhuriyet Uni-

versity Faculty of Medicine Ethics Committee (26/06/2014, nu.2014-06/10). After obtaining the permissions, the patients were informed about the study according to the Informed Voluntary Consent Form and their consent was obtained.

3. Results

The median age of the patients included in the study was 63 (minimum 48 - maximum 78) for males and 67.5 (minimum 51 - maximum 72) for females. A total of 20 knees, including the left knee of six patients, the right knee of 12 patients and both knees of one patient, were included in the study.18 patients underwent primary prosthesis in external centers and two patients underwent primary prosthesis in our clinic, and the indication for primary prosthesis was osteoarthritis. In the first stage operation, removal of the infected material, debridement and spacer placement were performed. New prosthesis implantation in the second stage was performed in 18 knees, but could not be performed in two patients. One of the 18 knees that underwent revision resulted in fistulising osteomyelitis despite all treatment applications and arthrodesis was performed. Another patient underwent a two-stage revision knee replacement procedure.

When we looked at the comorbidities of the 19 patients diagnosed with infected knee prosthesis; nine patients had diabetes, five patients had diabetes and hypertension, one patient had Parkinson's disease, and one patient had aortic and mitral valve replacement. In the next part of the findings, 17 knees of 16 patients who underwent two-stage revision as a result of an infected knee prosthesis and three patients who underwent arthrodesis will be reviewed. The median time from the application of the spacer to the second-stage operation was 68 days (minimum 41 to maximum 214) for both male and female patients. This period was median 71 days (minimum 41 to maximum 214) in men and median 67 days (minimum 48 to maximum 158) in women.

When the follow-up periods of male and female patients after the second stage surgery were evaluated, the median follow-up period was found to be 17 months (minimum 6.5 - maximum 102). This period was median 14 months (minimum 7,5 - maximum 102) in male patients and median 17 months (minimum 6,5 - maximum 32) in female patients (p=0,045). The ages, infection periods, follow-up periods and genders of the study patients are given comparatively in **Table 1**.

ESR, CRP and WBC parameters were evaluated as infection parameters. At the end of follow-up, a significant improvement in infection markers was observed: ESR decreased from 52.35 ± 25.7 mm/hour pre-spacer to 29.52 ± 12.16 mm/hour (p<0.001), while CRP decreased from 50.34 ± 54.39 mg/dL to 8.12 ± 4.49 mg/dL (p<0.001). WBC showed no significant change during follow-up (p=0.079). When we compared these values statistically, the lower CRP value before revision compared to the CRP value before spacer was significant with p<0.001. However, when we compared the CRP value at follow-up with the CRP value before revision, the p value was found to be p=0.011 (**Table 2**).

When the white blood cell values were analyzed, it was observed that the mean WBC value before spacer was 9428 ± 3757.92, the mean WBC value before revision was 7228 ± 1408.42, and the mean WBC value at follow-up was 7357 ± 1373.18. When these results were compared statistically, the p value between the first and second values was found to be p<0.001 and the p value between the second and third values was found to be p=0.079.

According to the culture results obtained perioperatively in the first stage; *Staphylococcus aureus* was grown in four patients, *Staphylococcus epidermidis* in three patients, *Pseudomonas aeruginosa* in two patients and *Gemella species* in one patient. There was no growth in the remaining seven patients.

The American Knee Society clinical and functional scores improved significantly, with clinical scores increasing from 53.29 ± 9.51 preoperatively to 83.21 ± 9.51 postoperatively (p<0.001) and functional scores rising from 40.88 ± 20.48 to 63.23 ± 30.81 (p=0.018). Patients achieved a significant increase in range of motion, with mean flexion improving from 68.52° ± 19.34 to 92.64° ± 16.30 (p<0.001). Likewise, when the mean flexion contracture was evaluated, it was reduced from 7.05° ± 12.12 before revision to 1.76° ± 4.98 after revision (p=0.018).

Table 1

Age, sex, duration of infection, follow-up of patients

	Male Mean/Median	Female Mean/Median	p	Total Mean/Median
Age at time of primary TKR /year	56.5 ± 13.3 53 (40-77.5)	62.25 ± 6.4 63.25 (50.5-71)	0.067	60.1 ± 9.6 62.5 (40-77.5)
TKR spacer interval/month	52.7 ± 52.02 47 (0.75-120)	31.1 ± 24.2 26.5 (1-79)	0.049	39.8 ± 38.1 26.5 (0.75-120)
Spacer revision time / day	101.2± 59.8 71 (41-214)	82.7 ± 35.6 67 (48-158)	0.099	90.35 ± 46.34 68 (41-214)
Period of follow-up/month	27.6 ± 33.3 14 (7.5-102)	19.1 ± 9.2 17 (6.5-32)	0.045	22.6 ± 21.96 17 (6.5-102)

TKR: Total knee replacement

Table 2

ESR, CRP, WBC means and statistical comparisons

	Before Spacer	Before Revision	Follow-up	p
ESR±SD (mm/hour)	52.35 ± 25.7a	33.70 ±13.61b	29.52 ±12.16c	p(a-b):<0.001 p(b-c):0.027
CRP±SD (mg/dl)	50.34± 54.39a	9.59 ±8.57b	8.12 ± 4.49c	p(a-b):<0.001 p(b-c):0.011
WBC±SD (mm3)	9428 ±3757	7228 ±1408	7357 ± 1373.18	p(a-b):<0.001 p(b-c):0.079

CRP: C - reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White Blood Cell

4. Discussion

Total knee arthroplasty (TKA) is a surgical treatment method that is increasingly used in the world and in our country for the treatment of problems of the knee that cannot be solved with medical treatments, with successful results[9]. Diabetes, hypertension, rheumatoid arthritis, increased body mass index and steroid therapy have been shown to be major risk factors for infection after primary total knee arthroplasty[6]. When we look at the 19 patients with infected TKA in our study, we see that nine patients had diabetes and five patients had diabetes and hypertension, supporting that diabetes is a risk factor. ESR, CRP, WBC values are important in the diagnosis of infection. These parameters increase after surgical trauma even in the absence of infection and return to normal within weeks. Here, it is important that CRP value returns to normal more rapidly than ESR. Studies emphasize that ESR above 30 mm/hour and CRP above 20 mg/l should be interpreted in favor of infection[10].

Our study highlights the clinical utility of CRP and ESR as reliable markers for monitoring infection resolution during two-stage revision. The significant decrease in CRP values pre- and post-revision ($p<0.001$) supports its role as a sensitive indicator, consistent with findings in the literature. In contrast, WBC showed minimal changes and lacked statistical significance during follow-up, reflecting its limited specificity in diagnosing periprosthetic infections, as reported by Toossi et al. (2012)[11]. There is still inconsistency about the effectiveness of WBC values in distinguishing septic and aseptic loosening. There are studies reporting that preoperative WBC values are within the normal range in cases. CRP is reported in the literature to have high specificity and sensitivity. Since it has been reported that the CRP value alone can be misleading, it supports other clinical and laboratory findings. Although the ESR value is affected by many factors, it is included among the diagnostic criteria for various periprosthetic joint infections as a criterion supporting infection[12-15].

The gold standard for the diagnosis of infection is the examination of deep tissue cultures obtained intraoperatively[16]. In our study, intraoperative cultures were obtained during the first stage from all patients in whom two-stage revision was planned. Care was taken to obtain samples from at least three different sites from each patient. Despite this, 12 of 20 knees of 19 patients (60%) were cultured. There was no growth in eight knees (40%). In the literature, even if all the rules to be considered during culture collection are followed, the growth rate in cultures obtained is reported to be 65-94%[17]. 18 of 20 knees diagnosed with infected knee prosthesis should receive oral or parenteral antibiotherapy before admission, and antibiotherapy should be discontinued for at least two weeks before culture is taken; however, we believe that our culture results caused less growth than the rate stated in the literature because the optimum time could not be provided due to the heavy clinics of the patients and the density of patients requiring operation.

Staphylococcus aureus (22%), *coagulase-negative staphylococci* (22%), *alpha- and beta-haemolytic streptococci* (9% and 5%), *enterococci* (7%), *aerobic Gram-negative bacilli* (25%) and *anaerobes* (10%) were the most common microorganisms found in infected knee arthroplasties[18]. In our study, *Staphylococcus aureus* was grown in five patients, *Staphylococcus epidermidis* in four patients, *Pseudomonas aeruginosa* in two patients and *Gemella Species* in one patient.

When we examine the antibiotics used in the cement, we see that the use of vancomycin, tobramycin, teicoplanin, gentamicin is concentrated in the literature[19]. We used antibiotic cement prepared by adding 2 g teicoplanin to cement containing 40 g gentamicin in all our patients in accordance with the literature. No toxicity was seen in any of our patients and the infection was eradicated except for one patient who ended up with arthrodesis.

When the literature is analyzed in terms of the waiting time between the two stages, it is seen that there is actually no consensus on this period[20]. Although it is concluded that it will be difficult to eradicate the infection if this interval is short; it has been shown that long interval periods increase the rate of recurrent infection. In addition, it is known that bone mineral density decreases and muscle atrophy is more common in long interval periods, which makes rehabilitation difficult after the second stage operation. It has also been reported that the cost of treatment increases and patient satisfaction decreases due to long treatment times[21]. When we consider that the mean interval between the two stages in our patients was 90.35 days and the median was 68 days, we see that although it seems long at first glance according to the literature, it does not go beyond the given limits. The reasons for this long interval include the difficulty in ensuring the eradication of the infection due to the absence of culture growth in nearly half of our patients and empirical antibiotic treatment, the fact that one patient received treatment for deep vein thrombosis and two patients received treatment for urinary tract infection before revision, and the fact that our patients could not come to the controls at the desired times due to referral problems.

A 91% success rate was reported in the mid-long term results of another 71 centers in which two-stage revision was performed in 96 infected knee prostheses[22]. When we look at our patients, success was achieved in 16 of 18 knees in which two-stage revision was performed. In one patient, infection was observed in the early period and was treated with debridement and antibiotherapy, but arthrodesis was performed as it resulted in fistulized osteomyelitis with discharge in the follow-up. One of our patients underwent a second two-stage revision surgery due to reinfection. In this patient, the cause of reinfection was urinary tract infection secondary to hy-

pospadias and urinary tract infection was treated before the second revision and the infection was eradicated in the follow-up. After this case, complete urinalysis was routinely performed in all patients before both primary and revision surgeries. After two-stage revision surgery, 94% success rate was achieved and this rate is compatible with the literature. The results of two-stage surgery performed by Petis et al. on 245 infected total knee arthroplasties support the success of this method[23].

In the literature, non-infectious complications included aseptic loosening (19.7%), instability (11.6%), osteolysis (10.4%), arthrofibrosis (8.1%), polyethylene abrasion (7.7%), malposition (5.4%), patellar complication (3.1%), periprosthetic fracture (2.3%), pain (1.5%) and lack of extensor mechanism (0.8%)[24]. In our patients, one medial condyle fracture was seen as a complication and was fixed with a plate-screw, and one patient developed deep vein thrombosis during follow-up after the first stage. These complications, which are also seen in primary knee replacement operations, are within acceptable limits. Arthrodesis can be performed after unsuccessful total knee arthroplasty, loss of the extensor mechanism, or highly virulent periprosthetic infections that cannot be eradicated[25]. One of the patients in this study underwent arthrodesis because the infection could not be treated.

In this study using the American Knee Society scoring system, the mean preoperative clinical score increased from 53.29 (SD 9.51) to 83.21 (SD 9.51) postoperatively ($p<0.001$). The significant improvement in functional scores (40.88 to 63.23; $p=0.018$) and range of motion (68.52° to 92.64°; $p<0.001$) underscores the efficacy of two-stage revision in restoring joint function. These results align with Haleem et al.'s (2004) reported success rates of 91% for infection eradication, further validating this approach as the gold standard for managing infected TKAs.[22]. When we analyzed the flexion contracture, it was found that it decreased from 7.05° (SD 12.12) preoperatively to 1.76° (SD 4.98) postoperatively ($p=0.018$). Both the increase in range of motion and the improvement in flexion contracture were found to be consistent with the literature (Table 3). In the study conducted by Petis et al., improvement in knee scores was observed after two-stage revision surgery[23].

The pain score, another parameter we evaluated in our patients, decreased significantly postoperatively. While we had six patients with severe pain preoperatively, there were no patients with severe pain postoperatively. Similarly, walking distances increased significantly postoperatively. Preoperatively, two patients could not walk and seven patients could walk at home, postoperatively there were no more patients who could not walk and the number of patients who could walk at home decreased to two. This study's retrospective nature and single-center design limit the generalizability of the findings. Future research should focus on prospective, multicenter trials comparing one-stage and two-stage revisions. Additionally, evaluating long-term outcomes and cost-effectiveness would provide further insights into optimizing treatment protocols.

5. Conclusion

Antibiotics were given to our patients for the agents grown in the culture. If there was no growth in the culture, antibiotherapy was empirically organised to cover the most common agents *Staphylococcus aureus* and *Staphylococcus epidermidis*. The drugs were administered intravenously for at least two weeks and, if necessary, six weeks. In the following periods, antibiotherapy was discontinued or continued according to the clinical examination of the knee, ESR and CRP results.

This study demonstrates that two-stage revision arthroplasty is an effective and reliable method for managing infected total knee arthroplasty, achieving a 94% infection eradication rate and significant improvements in clinical and functional outcomes. The reduction in CRP and ESR levels pre- and post-revision underscores the utility of these markers in infection monitoring. Furthermore, the observed improvements in range of motion and flexion contracture highlight the procedure's potential to restore joint function. Our findings align with existing literature, supporting two-stage revision as the gold standard treatment for infected TKA. However, the relatively long spacer-to-revision intervals in this cohort emphasize the need for careful infection monitoring and individualized treatment planning. The study's retrospective nature and single-center design limit the generalizability of these findings, underscoring the need for prospective, multicenter studies to evaluate long-term outcomes and optimize treatment protocols. Future research should focus on comparing one-stage versus two-stage revisions and exploring strategies to reduce spacer intervals without compromising infection control.

Statement of ethics

This study was approved by the Ethics Committee of Cumhuriyet University Faculty of Medicine Ethics Committee (26/06/2014, nu.2014-06/10) The study was performed according to the Declaration of Helsinki.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

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Author contributions

All authors contributed to the article.

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Risk Factors for Treatment Resistant Postoperative Surgical Site Infections

Hayal Uzelli Şimşek[1], Firdaus Mamleeva[1], Ercan Koçkaya[1], Özge Senem Yücel Çiçek[1]

1 Kocaeli University School of Medicine, Department of Obstetrics and Gynecology, Kocaeli, Türkiye

Abstract

Aim: Surgical site infection (SSI) is the most common complication seen after surgery. The aim of this study was to determine the risk factors that cause resistance to antibiotic treatment for SSI.

Methods: All patients' records who underwent elective gynecologic surgery between 2021-2023 at the Department of Obstetrics and Gynecology, Kocaeli University were scanned. Patients who had positive surgical site culture were enrolled in the study. Control culture data taken after antibiotic therapy were recorded. The demographic, obstetric and perioperative characteristics were compared between culture negative (control group) and culture positive (study group) patients.

Results: Patients with positive cultures were included in the study. There was a significant difference in terms of chronic medication between the two groups(p=0.002). The duration of hospitalization before SSI development was also significantly higher in the study group(p=0.017). A significant difference was found between the 2 groups in terms of the number of antibiotics used for the treatment of SSI(p=0.027). The use of multi-antibiotic regimens was more common in the study group.

Conclusion: The use of oral antidiabetic drugs and prednisolone was higher and the duration of hospital stay was longer in patients that developed treatment-resistant SSI. The need for multi-antibiotic regimens based on initial culture results was more common in the study group. In order to reduce the incidence of treatment-resistant SSI in patients undergoing planned surgery, a throughout evaluation of the patient is essential. Clinicians should take into consideration the risk of treatment-resistant infection in SSI patients with chronic medication use, long hospital stay, and infections requiring multi-drug regimens.

***Keywords**: Gynecological surgery; surgical site infection; surgical site culture; resistance to antibiotic therapy*

1. Introduction

Every surgeon tries to perform surgery in the best way possible without causing any complications or harm to the patient. However, despite all possible efforts, perioperative or postoperative complications that increase patient morbidity may occur in any surgery. Surgical site infections (SSI) are just one of these complications[1]. SSI is the most common complication after gynecologic surgeries[2] and it has been shown that SSI develops at a rate of 2.7% after hysterectomy[3]. SSIs are superficial or deep infections that occur in the surgical area within one-month postoperatively[4]. Thus, predictors of post-operative SSI after gynecological surgery are of clinical benefit. This will also help when preparing guidelines for future reference[1].

Although defining risk factors for SSI is complex and difficult, there are numerous published studies concerning the risk factors[1,2,5,7]. However, the number of studies examining predictive factors for SSIs resistant to treatment in gynecologic surgery is quite low. When looking at the literature, modifiable factors, such as preoperative anemia, malnutrition, smoking, obesity, hypertension (HT), type 2 diabetes mellitus (DM) and unmodifiable predisposing factors such as age and malignancy have been identified for SSI[4]. If these factors are controlled as well as possible in the preoperative period, the risk of SSI may be reduced. If anemia is present, iron supplementation (or blood transfusion if time is limited), identifying and resolving the cause of malnutrition and applying total parenteral nutrition pre- and postoperatively if necessary, reducing or smoking cessation, ensuring weight loss if body mass index (BMI) is high, controlling HT and DM, using prophylactic antibiotics, and ensuring tissue oxygenation and normothermia in the intraoperative period have been shown to reduce the occurrence rate of SSI[4,8]. In obese patients, it is also recommended not to leave subcutaneous dead space and, if necessary, to use a negative pressure drain in this area[9].

The resistance of SSIs to antibiotics has been less well investigated, Therefore, we aimed to examine and identify the risk factors for patients who develop resistance to treatment which results in

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higher morbidity and mortality rates compared to patients who respond to treatment. If it is known which reasons cause resistance to treatment in patients who develop SSI, the success of the treatment can be achieved by correcting the modifiable factors or increasing attention in the presence of these factors.

2. Materials and Methods

This study was approved by the Kocaeli University non-invasive ethics committee (KU GOKAEK-2024/277). All patients between the ages of 18 and 90 years who underwent elective surgery for benign or malignant gynecological reasons between January 2021 and December 2023 in the Department of Obstetrics and Gynecology, Kocaeli University Hospital, Türkiye, were retrospectively screened for the presence of SSI. Patients who underwent wound culture after developing SSI findings and only those in whom growth was detected were included in the study. In our clinic, 1 g of cefamezin is routinely given to all patients preoperatively and control cultures are routinely taken from patients who are given appropriate antibiotic therapy after SSI. Demographic, obstetric and perioperative data of patients with positive control culture (study group) and patients with negative control culture (control group) were compared.

Table 1

Demographic, obstetric and perioperative data of all patients

	Study Population (n=144)
Age, median (IQR)	53 (40-65)
BMI, median (IQR)	34.75 (29.85-41.45)
Gravidity, median (IQR)	3 (2-4)
Parity, median (IQR)	2 (1-3)
Abortion, median (IQR)	0 (0-0.75)
Number of living child, median (IQR)	2 (1-3)
Postmenopause, n (%)	81 (%56.3)
Hypertension (HT), n (%)	75 (%52.1)
Diabetes mellitus (DM), n (%)	62 (%43.1)
Oral antidiabetic, n (%)	37 (%58.9)
Insulin, n (%)	9 (% 12.5)
Prednisolone, n (%)	3 (%5.1)
Malignancy, n (%)	67 (%46.5)
Use of LMWH, n (%)	117 (%81.3)
Operation time (minutes), median (IQR)	95 (75-133.75)
Blood transfusion, n (%)	18 (%12.5)
First culture growth, n (%)	144 (%100)
Second culture growth, n (%)	49 (%34)

BMI: Body mass index; LMWH: low-molecular-weight heparins; $p<0.05$ is significant.

Patients who had local or systemic infectious symptoms, such as redness, increased temperature, and itching in the area where surgery would be performed before the operation, patients who had a culture taken because of infection in the wound area in the postoperative period but were using antibiotics at the time, and patients who were found to have developed SSI but no positive cultures were found were not included in the study.

The patients' age, BMI, indications for surgery, obstetric and gynecological history, menopause status, comorbidities, medications used, surgical approach types (Pfannenstiel, lower midline incision, midline incision, vaginal and laparoscopic approach), whether postoperative low molecular weight heparin (LMWH) was administered, surgery duration, amount of blood transfusion if administered, whether pathology results were benign or malignant, number of days of hospitalization, wound culture results, and whether secondary suture was required were recorded.

According to the culture results, single, double, triple or quadruple antibiotic combinations were selected according to their antibiograms and based on indicated sensitivities and were used in all patients.

Statistical evaluation was performed using IBM SPSS, version 29.0 (IBM Corp., Armonk, NY, USA). The normal distribution test was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov tests. Numerical variables are given as Mean ± standard deviation, median (25th-75th percentile) and frequency (percentages). Differences between groups/materials were compared using Student's t test, One-way analysis of variance and Tukey's multiple comparison test for numerical variables with normal distribution and Mann Whitney U Test, Kruskal Wallis test and Dunn's multiple comparison test for numerical variables without normal distribution. Fisher's exact chi-square test, Yates' chi-square test and Monte Carlo chi-square test were used for categorical variables to evaluate the differences between groups. The relationship between numerical variables was evaluated using Spearman or Pearson correlation analysis, as appropriate. Logistic regression analysis was performed to determine risk factors for treatment-resistant wound infections. A $p<0.05$ was considered sufficient for statistical significance in two-sided tests.

Table 2

The growth percentages of the agents in the wound culture of all patients are given.

Bacterial Agents	n (%)
Escherichia coli	39 (%22.8)
Enterococcus faecalis	35 (%20.5)
Klebsiella pneumonia	20 (%11.7)
Staphylococcus aureus	13 (%7.6)
Pseudomonas aeruginosa	13 (%7.6)
Enterobacter cloacae	8 (%4.7)
Other Staphylococcus species	22 (%12.8)
Others*	21 (%12.3)

** Other agents included Proteus mirabilis, Morganella morgagni, Streptococcus agalactiae, Serratia marcescens, Klebsiella aeroginosa.*

3. Results

Demographic, obstetric and perioperative data of the patients are given in **Table 1**. A total of 144 patients who developed postoperative SSI and had positive wound cultures were identified. The median (range) age of the patients was 53 (40-65) years, ranging from 22-89 years old. The median BMI was 34.75 (29.85-41.45) kg/m^2 and 105 (72.9%) of the patients were obese (BMI ≥30 kg/m^2). More than half were postmenopausal (n=81, 56.3%). The number of patients with both cultures positive was 49 (34%). **Table 2** shows the percentage of growth of the agents in the wound culture of the patients.

The types of operations performed on the patients are shown in **Table 3**. The most common operation was hysterectomy ± unilateral/bilateral salpingooophorectomy ± bilateral pelvic paraaortic lymph node dissection (BPPALND) ± omentectomy due to malignancy. Histopathological reports confirmed that 67 (46.5%) of the patients were operated on for malignant causes. The median operation time was 95 (75-133.75) minutes.

Table 3

Types of operations performed on patients in both groups.

Operations	n (%)
Hysterectomy ± unilateral/bilateral salpingo-oophorectomy ± BPPLND ± omentectomy (Malignant cause)	68 (%47.2)
Hysterectomy ± unilateral/bilateral salpingo-oophorectomy (Benign cause)	36 (%25.0)
Myomectomy	11 (%7.6)
Oophorectomy (unilateral/bilateral)	5 (%3.5)
Salpingectomy (unilateral/bilateral)	3 (%2.1)
Ovarian cyst excision	8 (%5.6)
Vulvectomy (malignant)	7 (%4.8)
Vaginal hysterectomy ± unilateral/bilateral salpingo-oophorectomy	3 (%2.1)
Other vaginal procedures	3 (%2.1)

BPPLND: bilateral pelvic and paraaortic lymph node dissection.

Table 4

Comparison of demographic, obstetric and medical history data of the patients between the two groups.

		Control group (n=95)	Study group (n=49)	p
Second culture growth, n (%)		0 (%0)	49 (%100)	<0.001
Age, median (IQR)		52 (41-65)	54 (37.5-64.5)	0.835
BMI, median (IQR)		35 (29.4-41)	33.3 (30.2-42.2)	0.647
Obesity, n (%)		67 (%70.5)	38 (%77.6)	0.483
Gravidity. median (IQR)		3 (2-5)	2 (1.5-3)	0.152
Parity, median (IQR)		2 (1-4)	2 (1-3)	0.172
Abortion, median (IQR)		0 (0-1)	0 (0-0.5)	0.973
Number of living child, median (IQR)		2 (1-3)	2 (1-3)	0.189
Postmenopause, n (%)		52 (%54.7)	29 (%59.2)	0.740
Hypertension (HT), n (%)		44 (%46.3)	31 (%63.3)	0.080
Diabetes mellitus (DM), n (%)		36 (%37.9)	26 (%53.1)	0.118
Drugs, n (%)	OAD	17 (%18.0)	20 (%40.9)	0.002
	Insulin	6 (% 6.4)	3 (%6.1)	
	Prednisolone	1 (%1.1)	2 (%4.0)	

OAD: Oral antidiabetics; BMI: Body mass index; p<0.05 is significant.

Demographic, obstetric and history data of the patients are compared between the two groups in **Table 4**. While the number of patients with growth in only the first culture was 95 (66%), the number of patients with growth in both cultures was 49 (34%). No significant difference was found in terms of age, BMI, obstetric data, presence of menopause, HT and DM diagnoses between these two groups. However, there was a significant difference between the groups in terms of chronic drug use (p=0.002).

Table 5 compares the data of the groups in the preoperative and postoperative follow-ups. No significant difference was found in terms of surgical approach. No significant difference was found in terms of being operated on due to malignancy, operation times, blood transfusion requirements and postoperative LMWH use. The median hospital stay before the development of SSI was significantly longer in the study group (p=0.017). A significant difference was found in the number of antibiotics used in the treatment of SSI between the two groups (p=0.027). The use of triple and quadruple antibiotic regimens was more common in the study group. No significant difference was found in terms of the need for secondary sutures.

Table 5

Comparison of peroperative and postoperative follow-up data between the two groups.

	Control group (n=95)	Study group (n=49)	p
Surgical approach, n (%)			
Pfannenstiel incision	19 (%20.0)	12 (%24.5)	
Lower midline incision	23 (%24.2)	11 (%22.4)	0.796
Midline incision	37 (%38.9)	18 (%36.7)	
Vaginal intervention	10 (%10.5)	3 (%6.1)	
Laparoscopic intervention	6 (%6.3)	5 (%10.2)	
Presence of malignancy, n (%)	43 (%45.3)	24 (%49.0)	0.805
Operation time (minutes), median (IQR)	95 (75-130)	100 (75-145)	0.499
Blood transfusion, n (%)			
·1 Unit	6 (%6.3)	4 (%8.2)	
·2 Unit	3 (%3.2)	0 (%0)	
·3 Unit	2 (% 2.1)	0(%0)	0.446
·4 Unit	1 (% 1.1)	1 (%2.0)	
·5 Unit	0(%0)	1 (%2.0)	
Use of LMWH (postoperative), n (%)	75 (%78.9)	42 (%85.7)	0.447
Length of stay (days), median (IQR)	5 (4-9)	8 (4-18.5)	0.017
Antibiotic treatment given according to the first culture, n (%)			
·Single	72 (%75.8)	34 (%69.4)	0.027
·Double combination	18 (% 18.9)	6 (% 12.2)	
·Triple combination	5 (% 5.3)	6 (% 12.2)	
·Quadruple combination	0 (% 0)	3 (% 6.1)	
Secondary suture requirement, n (%)	7 (%7.4)	7 (%14.3)	0.236

LMWH: Low-molecular-weight heparins; p<0.05 is significant.

4. Discussion

SSI, which affects surgical treatment outcomes, is the most common hospital-acquired infection[2]. The incidence of SSI after obstetric and gynecologic surgery is between 4.6% and 10.3%[1,2]. However, defining risk factors for SSI is complex and difficult. Current findings in the literature on risk factors are generally limited due to small sample sizes and poor statistical power[2].

In the present study, and unlike in other studies examining infection risk factors, all patients who had already had growth were included, but the risk factors of patients who had growth in the sec-

ond culture despite appropriate treatment according to identified antibacterial sensitivities were investigated. In a meta-analysis including 13 articles for SSI in gynecology, BMI ≥24, malignant lesions, ≥60 minutes of surgery, ≥300 mL of intraoperative bleeding, urinary catheter retention time and ≥3 vaginal digital examinations were reported as independent risk factors for SSI in obstetric and gynecological surgery[2]. Our findings support these data with nearly three-quarters of our cohort being obese, more than half were operated for malignant reasons and the median surgery time was longer than one hour. However, only 18 (12.5%) patients required blood transfusion. In a study including 206 Caesarean section operations, controlling BMI, shortening the operation time, good bleeding control, and reducing the duration of urinary catheterization were found to be beneficial in preventing SSI[5].

In gynecological operations, incisions are usually applied to the skin, vulva, vagina, umbilical region and other areas where many microorganisms are found. These incisional surgical approaches are significant in terms of infection[2]. The operations with the lowest SSI rate are laparoscopy and sterilization (tubal ligation) surgeries. The highest infection rate was seen in radical and extended hysterectomies. In addition, it has been suggested that vaginal hysterectomy (1%) has a lower SSI incidence than abdominal surgery (5.7%)[10]. Abdominal distension frequently occurs in the early postoperative period and therefore the wound layers are subjected to significant tension. From this perspective, it has been suggested that more frequent use of transverse incisions will greatly reduce the incidence of both hernia and wound infection complications[10]. We also added the types of abdominal incisions applied to the patients and the vaginal approach rates to the study for comparison. However, we found that these differences were not a risk factor in terms of the development of resistance to treatment in SSIs.

The immune system is generally at risk in patients with malignant tumors and SSIs are frequently seen in these patients[2]. However, in the present study, malignancy was not found to be a risk factor for resistance to treatment. It has been reported that HT is not a risk factor for SSI[1,6]. Our results support this as HT was not a risk factor for resistance to treatment. While DM is considered a risk factor for SSI in many studies[11-15], such a finding was not reported others[1,2,6,7,16]. Our findings also suggest that that DM was not a risk factor for SSIs in the study group. When we compared the BMIs and the number of obese patients between the two groups, there was no significant difference and that SSIs were not a risk factor for resistance to treatment. Other studies have also found that high BMI was not a risk factor for SSI[16]. However, the meta-analysis of SSI in gynecological surgery reported that BMI ≥24 kg/m2 conferred a 2.5 greater risk of SSI, BMI >28 a 16-fold increase in risk and and BMI >30 a 7-fold increase in risk[2]. In addition to its anti-inflammatory and hyperglycemic effects, single-dose dexamethasone administration did not increase the risk of SSI (p=0.19)[18]. However, in our study, it was found that chronic prednisolone and oral antidiabetic use was significantly more common in the group that developed treatment-resistant SSI.

The duration of surgery (>1 hour or >1.5 hours) has been identified as a risk factor for SSI in several studies (1,2,5,10). In the present study, the median duration of surgery was calculated as around 1.5 hours. However, when we evaluated the resistance to treatment in SSI by comparing the two groups, no significant difference was found. The hemoglobin value of all patients who underwent surgery was above 10 mg/dL. However, it was observed that some patients had to be transfused with erythrocyte suspension, varying from 1-5 units, in the postoperative period. When the two groups were compared, no significant difference was found in terms of transfusion requirement. When the literature was examined, the need for blood transfusion was given as a risk factor for SSI[1,2], and the need for blood transfusion is common in women with SSI (23.75%)[10]. However, another study stated that the need for blood transfusion was not a risk factor for SSI[16].

Infection is associated with increased hospital stay and therefore increased healthcare costs[2]. Studies have shown that a longer duration of hospitalization is associated with SSI that occurs later[19,20]. Our findings support this in the group that developed treatment-resistant SSI. It has been reported that the proportion of patients who required secondary sutures after SSI was high at 87.7%[4]. In the present study, secondary sutures were needed in only 14 patients and no significant difference was detected between the two groups for this procedure. This suggests that the presence of resistant SSI does not predict the need for secondary sutures.

5. Conclusion

In the present study, chronic drug use, multiple antibiotic treatment and long hospital stay before the development of SSI were evaluated as risk factors for treatment-resistant SSI. Clinicians should consider the possible risk of treatment-resistant infection in SSI patients who have a history of chronic drug use, especially steroids and oral anti-diabetic therapies, having long-term hospital stay pre-operatively and/or with a history of multiple antibiotic treatment regimens

Statement of ethics

This study was approved by the Ethics Committee of Kocaeli University non-invasive ethics committee (KU GOKAEK-2024/277)The study was performed according to the Declaration of Helsinki.

Source of Finance

The authors declare that they have received no financial support for this study

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The data supporting the conclusion of this article will be available by the authors without undue reservation.

Author contributions

All authors contributed to the article.

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Impact of COVID-19 Waves and Lockdowns on Emergency Department Visits and Intensive Care Unit Admissions in Türkiye: A Retrospective Analysis

Ayşe Ayyıldız[1], Fatih Alper Ayyıldız[2], Selim Yıldırım[3,4]

1 Eskişehir City Hospital, Department of Intensive Care, Eskişehir, Türkiye
2 Eskişehir City Hospital, Department of Emergency Medicine, Eskişehir, Türkiye
3 Anadolu University, Faculty of Economics and Administrative Sciences, Department of Economics, Eskisehir, Türkiye
4 Eskisehir Technical University, Faculty of Science, Statistics Department, Eskisehir, Türkiye

Abstract

Aim: This study aimed to evaluate the impact of the COVID-19 pandemic on emergency department (ED) utilization and intensive care unit (ICU) admissions in Türkiye, while also examining healthcare policies by focusing on changes in non-COVID-19-related visits during lockdown periods.

Methods: A retrospective analysis was conducted on ED and ICU admission data from a tertiary care hospital in Türkiye during the COVID-19 pandemic. Data were categorized into COVID-19 and non-COVID-19 cases and stratified based on curfew periods. The causal inference method, particularly Bayesian Structural Time Series modeling, was employed to evaluate trends in healthcare utilization and to question the reliability of the findings.

Results: Non-COVID-19 emergency department (ED) visits significantly decreased during the pandemic (p=0.00075), with the most notable reductions during lockdowns (p=0.00084). In the first lockdown, ICU admissions increased significantly (p=0.00029), while COVID-19 ED visits remained unchanged (p=0.09358). During the second lockdown, COVID-19 ED visits rose (p=0.000001), non-COVID-19 visits decreased (p=0.00019), and ICU admissions showed a non-significant numerical decline (p=0.10771). These findings indicate shifts in healthcare utilization and critical care demands during the pandemic.

Conclusion: The COVID-19 pandemic significantly altered healthcare utilization patterns, reducing non-COVID-19 ED visits without affecting ICU admission rates. These findings underscore the need for robust public health strategies, including improved triage systems and public education, to optimize healthcare delivery during crises. Further research is warranted to assess the long-term implications of delayed care for non-COVID-19 conditions.

***Keywords**: Emergency Department Utilization, COVID-19 Pandemic, Intensive Care Units*

1. Introduction

Emergency services are a critical part of hospitals where patients can access healthcare services 24 hours a day, 7 days a week. According to the circular numbered 31952 dated 13.09.2022 of the General Directorate of Treatment Services of the Ministry of Health of the Republic of Türkiye, 'It is essential that all patients applying to emergency services are evaluated as emergency patients upon their first application and admitted to emergency services and that procedures are carried out accordingly', the complaints that the patient states they have are accepted as emergencies until the physician examines and diagnoses them. Every patient who applies to the Emergency Service and states that they have urgent complaints is an emergency. They are definitely examined, treated, directed, admitted or referred according to their condition.[1] According to this circular, since the patient determines whether the patient is an emergency patient, a very serious workload has occurred in emergency services. This situation has reached such proportions that it can sometimes cause delays in the care of patients who really need it in emergency services.[2-4]

The COVID-19 pandemic has profoundly disrupted healthcare systems worldwide, leading to significant changes in patient behaviors, healthcare delivery, and resource allocation.[5,6] Emergency departments (EDs) and intensive care units (ICUs) have borne the brunt of these changes, serving as critical points of care during surges in COVID-19 cases.[7] Lockdown measures, implemented globally to curb the spread of the virus, have further influenced healthcare utilization patterns, including a marked reduction in

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non-COVID-related ED visits and shifts in ICU admission rate.[6,8]

In Türkiye, the effects of the COVID-19 pandemic on healthcare usage remain underexplored, particularly in the context of ED and ICU utilization during different pandemic waves and lockdown periods. Understanding these trends is essential for optimizing resource allocation, planning for future healthcare crises, and ensuring patient safety during public health emergencies.

This retrospective study aims to analyze ED visit volumes and ICU admission rates in Türkiye from 2019 to 2022, focusing on COVID-19 and non-COVID-related patterns during pandemic waves and lockdown periods. By leveraging Bayesian Structural Time Series (BSTS) methodology, we aim to provide robust causal inferences on the impact of these interventions on healthcare utilization.

2. Materials and Methods

This study was approved by the Eskişehir Education and Training Hospital of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 15.02.2023; Decision No: ESH/GOEK 2023/5). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

After obtaining ethics committee approval, the monthly number of non-COVID-19 and COVID-19 emergency department visits and intensive care admissions were retrospectively recorded between October 2019 and January 2022. The peak periods of the COVID-19 waves, as identified by the Ministry of Health of the Republic of Türkiye, were specifically noted and analyzed. According to the ministry's official data, the first wave occurred during March–May 2020, the second wave during September–November 2020, and the third wave during March–May 2021.[9]

The lockdown periods enforced by the Ministry of Internal Affairs of the Republic of Türkiye were determined based on official announcements.[10] The first major lockdown was implemented in May 2020, and the second in December 2020. The effects of these periods on emergency department visits and intensive care admissions were analyzed.

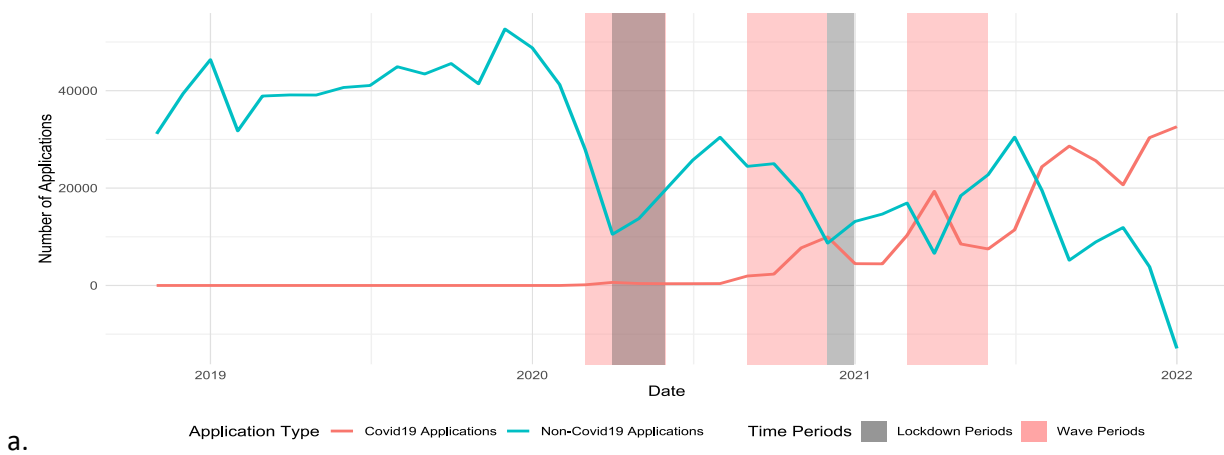
The number of non-COVID-19 emergency department visits in 2019, prior to the pandemic, was compared with the corresponding months in 2020 and 2021. During the pandemic, total emergency department visits were categorized into COVID-19 and non-COVID-19 groups for analysis.

2.1. Statistical Analysis:

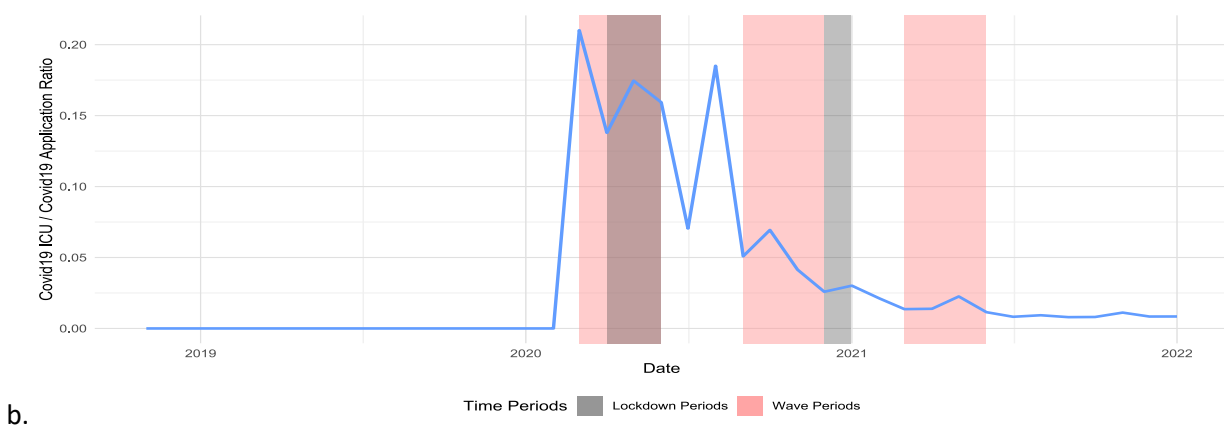
The Bayesian Structural Time Series (BSTS) methodology was employed for causal inference, particularly in the absence of randomized controlled trials. This method constructs counterfactuals using state-space time series models to estimate the causal impact of interventions. Pre-intervention data of the target metric were integrated with control series unaffected by the intervention, leveraging their predictive value.

Figure 1

Monthly time series graphics between 2019-2022
a) COVID 19 and NON-COVID 19 emergency department applications b) Intensive care admission rate



a.



b.

Table 1

Posterior inference on the impact of the COVID 19 ICU admission

	May 2020		December 2020	
	Average	Cumulative	Average	Cumulative
Actual	0.13	0.64	0.013	0.174
Prediction (s.d.)	0.0096 (0.031)	0.0482 (0.155)	0.043 (0.024)	0.556 (0.312)
95% CI	[-0.051, 0.071]	[-0.253, 0.357]	[-0.0045, 0.09]	[-0.0583, 1.18]
Absolute effect (s.d.)	0.12 (0.031)	0.59 (0.155)	-0.029 (0.024)	-0.381 (0.312)
95% CI	[0.057, 0.18]	[0.284, 0.89]	[-0.077, 0.018]	[-1.001, 0.233]
Relative effect (s.d.)	568% (347410%)	568% (347410%)	-75% (4175%)	-75% (4175%)
95% CI	[-6541%, 6235%]	[-6541%, 6235%]	[-214%, 115%]	[-214%, 115%]
Posterior tail-area probability p	0.00029		0.10771	
Posterior prob. of a casual effect	99.9712%		89%	

The BSTS framework incorporates a local-level random walk model and a regression component with static or dynamic coefficients, facilitating robust predictions. Predictor selection was optimized using a spike-and-slab prior, enabling efficient identification of relevant variables from large datasets. Causal effects were estimated using Markov Chain Monte Carlo (MCMC) sampling, which provided probabilistic estimates of intervention impacts.

Compared to traditional methods, BSTS excels in accounting for uncertainty, trends, seasonality, and automated covariate selection. It is a robust and flexible tool for causal inference in complex medical scenarios.[11]

According to this method, a statistically significant decrease in a post-lockdown series, or no significant difference between pre- and post-lockdown periods, indicates the effectiveness of the lockdown. A p-value < 0.05 was considered statistically significant.

.

3. Results

A significant decrease in non-COVID-19 emergency department visits was observed during the pandemic compared to pre-pandemic years (p=0.00075). In contrast, intensive care admissions were significantly higher during the first wave of the pandemic but gradually declined in subsequent months. The monthly time series analysis of emergency department visits and intensive care admissions is presented in **Figure 1**.

The findings for the first and second lockdown periods are detailed in **Table 1**.

During the first major lockdown, no statistically significant change was observed in COVID-19 emergency department visits (p=0.09358), while a significant decrease was noted in non-COVID-19 emergency department visits (p=0.00084). Intensive care unit (ICU) admissions, on the other hand, increased significantly (p=0.00029). The average COVID-19 ICU admission ratio during the post-lockdown period was approximately 0.13, compared to an expected response of 0.0096 in the absence of intervention (95% interval: [-0.051, 0.071]). The estimated causal effect was 0.12 (95% interval: [0.057, 0.18]), with a p-value of 0.00029, indicating that the first lockdown did not reduce COVID-19 ICU admissions. These results are detailed in **Figure 2**.

During the second major lockdown, a statistically significant increase was observed in the rate of COVID-19 emergency department visits (p=0.000001), whereas non-COVID-19 emergency department visits showed a significant decrease (p=0.00019). ICU admissions exhibited a numerical decrease, but this change was not statistically significant (p=0.10771). The average COVID-19 ICU admission ratio during the post-lockdown period was approximately 0.013, while the expected response without intervention was 0.043 (95% interval: [-0.0045, 0.090]). The estimated causal effect was -0.029 (95% interval: [-0.077, 0.018]), with a non-significant p-value of 0.10771. These results suggest that the second lockdown had a positive effect on reducing COVID-19 ICU admissions, as the increase observed prior to the lockdown did not continue. Detailed results for this period are shown in **Figure 3**.

Figure 2

Causal impact analysis for COVID-19 ICU admissions: model results for the effects of the first major lockdown (May 2020)

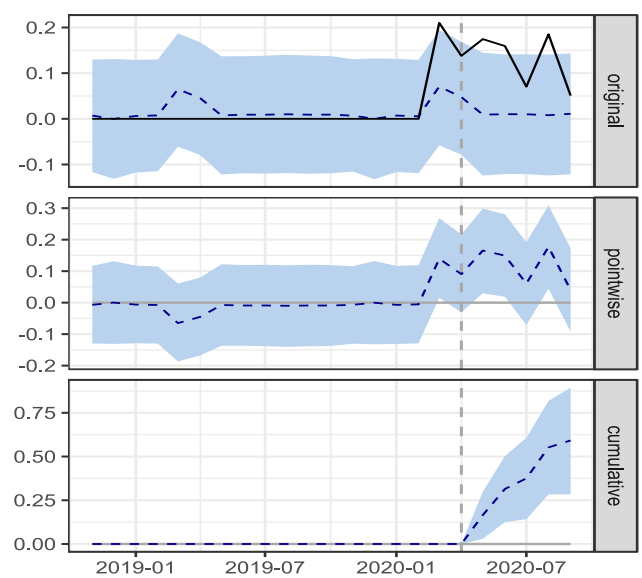
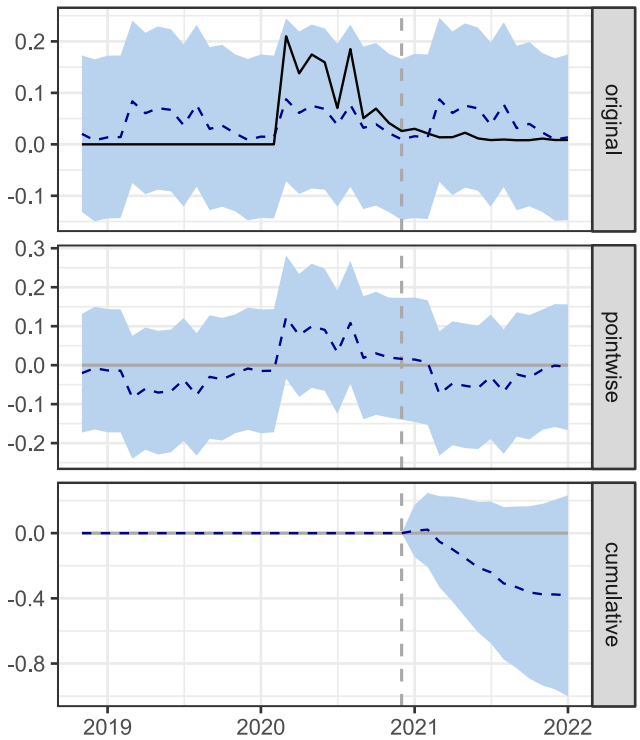


Figure 3

Causal impact analysis for COVID19 ICU admissions: model results for the effects of the second major lockdown



4. Discussion

Our study provides valuable insights into the impact of the COVID-19 pandemic on emergency department (ED) utilization and intensive care unit (ICU) admissions in Turkey. We observed a significant reduction in non-COVID-19 ED visits during curfew periods, which aligns with findings from other studies conducted globally. However, despite this decrease, ICU admission rates did not show a statistically significant decline during these periods, emphasizing the critical care demands imposed by the pandemic.

The reduction in non-COVID-19 ED visits can likely be attributed to factors such as fear of infection, government-imposed curfews, and public health policies encouraging individuals to delay or avoid seeking care unless absolutely necessary. This finding aligns with international reports, including studies from Canada (Rennert-May E), the Netherlands (Djik R), and Thailand (Yorsaeng R), which observed comparable reductions in ED utilization during lockdowns, attributed to patient hesitancy and alterations in healthcare-seeking behaviors.[12-14] A study conducted in Alberta, Canada, parallel to our study, examined changes in hospitalizations and ED visits before and after the implementation of public health measures during the COVID-19 pandemic, highlighting significant reductions in non-COVID ED visits and shifts in healthcare utilization patterns, likely due to delayed care or changes in patient behavior during lockdowns.[12] A large-scale observational study from three hospitals in the Netherlands focused on ED use during the first and second COVID-19 waves of the pandemic. They examined changes and rates in patient volumes, urgency classifications, and hospitalizations. The study attributed the reductions in ED visits in part to public health messaging and quarantine measures.[13] In our study, there were also significant decreases in non-COVID emergency room visits. We believe that the reasons for this are fear of infection, curfews and health policies.

A study from Thailand, while discussing the decrease in emergency room visits during quarantines, noted increases in ICU admissions and suggested that there were delays in presentation or care seeking behaviors for serious conditions during the restrictions. This study is consistent with our data.[14] In our study, although emergency room visits decreased, especially during quarantine periods, there was no actual decrease in seriously ill patients. ICU admissions did not change significantly. These decreases, while reducing ED crowding, may have delayed care for patients with critical non-COVID-19 conditions, leading to potential long-term health consequences.

Interestingly, while ED visits declined, ICU admissions during certain periods either remained stable or increased, as observed during the first major lockdown in our study. This trend highlights the challenges of managing healthcare resources during a pandemic, where balancing the care needs of COVID-19 and non-COVID-19 patients becomes increasingly complex. A detailed examination of the ICU admissions ratio using advanced causal inference methods, such as the Bayesian Structural Time Series (BSTS) model, has strengthened the reliability of our findings, providing a robust framework for evaluating intervention impacts.

Another important aspect of our findings is the shift in healthcare-seeking behavior, particularly in relation to inappropriate ED visits. In Turkey, ED overcrowding due to inappropriate visits is a well-documented issue, often driven by patients seeking faster service, quicker diagnostic results, or bypassing appointment delays in outpatient clinics. The COVID-19 pandemic significantly reduced these inappropriate visits, particularly among low-acuity (green area) cases, as supported by national and international studies.[4,6,8] This period underscores the potential for public health crises to reshape healthcare utilization patterns, offering insights into how effective patient education and streamlined triage systems can optimize ED use in the future.

Additionally, our study highlighted the crucial role of triage systems in managing ED workflow during the pandemic. In ideal conditions, triage systems direct patients to appropriate care levels based on urgency, yet variations in sociocultural factors, age, and regional differences can influence healthcare-seeking behavior. This discrepancy underscores the need for public awareness campaigns to educate individuals on appropriate ED usage and to promote primary care as a viable alternative for non-emergent issues. Studies from Turkey and other countries corroborate this need, highlighting the benefits of reducing inappropriate ED visits through targeted interventions.[15-18]

The COVID-19 pandemic also prompted significant shifts in healthcare policy and practice. The rapid adoption of telemedicine, enhanced community-based care, and increased reliance on primary care providers for managing stable COVID-19 cases demonstrate the healthcare system's adaptability during crises. These innovations, though born out of necessity, offer valuable lessons for addressing future public health emergencies, ensuring equitable access to care, and alleviating pressure on hospital-based services.[19]

Lastly, our findings suggest that the decreases in red and yellow area admissions during lockdown periods were partially influenced by external factors such as reduced traffic and decreased trauma cases due to limited mobility. However, the stable ICU admission rates indicate that critical care demands persisted, reinforcing the importance of maintaining robust ICU capacity during pandemics.

Future research should explore the long-term effects of delayed care for non-COVID-19 conditions and evaluate the effectiveness of policies aimed at optimizing healthcare delivery during crises. This includes refining triage systems, expanding public health education, and leveraging data-driven tools like BSTS models to guide

healthcare planning and decision-making.

4.1. Limitations of study

This study has several limitations that should be acknowledged. One of the primary limitations is the classification of emergency department visits into only two categories: COVID-19 and non-COVID-19 cases. While this approach provides a broad understanding of the pandemic's impact, it may overlook important nuances in patient presentations. A more detailed stratification of emergency department visits, such as categorizing patients based on triage levels (green, yellow, and red zones), could have provided a more granular understanding of the effects of the pandemic on emergency healthcare utilization. This would have allowed for a clearer assessment of the severity of conditions and better insights into how different acuity levels were affected during lockdown and non-lockdown periods.

Additionally, as this study relies on retrospective data, it is subject to inherent limitations such as the accuracy and completeness of medical records. Factors such as variations in triage protocols, changes in healthcare-seeking behavior, and potential underreporting during the pandemic could also influence the findings. Future studies incorporating real-time data collection and more detailed patient categorization could yield more robust and actionable insights.

5. Conclusion

This study highlights the significant impact of COVID-19 waves and lockdown measures on healthcare utilization in Turkey, with a marked reduction in non-COVID-19 emergency department visits and fluctuating ICU admissions. The findings underscore the need for adaptive healthcare strategies to address the dual burden of pandemic and non-pandemic care demands. Using Bayesian Structural Time Series methodology, this analysis provides a robust framework for evaluating interventions, offering valuable insights for optimizing resource allocation during future public health crises. Further research is warranted to explore the long-term consequences of these trends and improve resilience in healthcare systems.

Statement of ethics

This study was approved by the Eskişehir Education and Training Hospital of Medicine Non-Interventional Clinical Research Ethics Committee (Date: 15.02.2023 Decision No: ESH/GOEK 2023/5). All procedures were performed according to the ethical rules and principles of the Declaration of Helsinki.

Source of Finance

The authors declare that they have received no financial support for this study

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Author contributions

All authors reviewed the results and approved the final version of the manuscript.

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Pediatric Distal Tibial Physeal Injuries and Their Role in Premature Physeal Arrest: A Multi-Center Retrospective Study

Yasin Erdoğan[1], Ali Said Nazlıgül[2], Şahan Güven[3], Tural Talibli[1], Erkan Akgün[4], Enejd Veizi[3]

1 Department of Orthopedics and Traumatology, Ankara Etlik City Hospital, Ankara, Türkiye
2 Department of Orthopedics and Traumatology, Ankara Sincan Education and Research Hospital, Ankara, Türkiye
3 Department of Orthopedics and Traumatology, Ankara Bilkent City Hospital, Ankara, Türkiye
4 Department of Orthopedics and Traumatology, Ankara Private Etlik Lokman Hekim Hospital, Ankara, Türkiye

Abstract

Aim: To evaluate the impact of factors such as fracture type, initial displacement, reduction method, associated fibular fractures, and trauma mechanism on the occurrence of premature physeal arrest in pediatric distal tibial physeal fractures.

Methods: This retrospective study included 83 pediatric patients who underwent surgical treatment for distal tibial physeal fractures between 2019 and 2024 at two centers. Data on fracture type (Salter-Harris classification, McFarland, tillaux, triplanar), reduction method (open/closed), fixation technique, and mechanism of injury were analyzed. Angular deformities were assessed using lateral distal tibial angle (LDTA) and anterior distal tibial angle (ADTA). Statistical analysis was performed using SPSS software, with significance set at $p<0.05$.

Results: The cohort included 59 males (71%) and 24 females (29%) with a mean age of 12 years. Premature physeal closure was observed in 10 patients (12%), with higher rates in Salter-Harris type 4 (50%) and McFarland fractures (50%). One McFarland fracture resulted in varus deformity, necessitating corrective osteotomy. Among all distal tibial fractures, traffic accident-related injuries were significantly associated with higher rates of physeal arrest. The incidence of premature closure in triplanar and Tillaux fractures was 4.5% and 12.5%, respectively, consistent with literature data.

Conclusion: Salter-Harris type 4 and McFarland fractures, as well as high-energy trauma, are significant risk factors for premature physeal arrest. Patient education and close follow-up are critical for early detection and management of complications. Prospective, randomized studies are warranted to further elucidate these findings.

Keywords: *Pediatric, distal tibial fracture, physeal injury, lateral distal tibial angle, anterior distal tibial angle*

1. Introduction

Pediatric distal tibial physeal fractures are the most common injuries following distal radius and phalangeal physeal fractures [1]. They account for approximately 11-20% of all physeal fractures [2,3]. Inadequate reduction and joint incongruity may lead to premature physeal closure and deformities [4]. The rates of premature physeal closure following pediatric distal tibial physeal fractures can reach up to 38% [5].

During the rapid growth phase of childhood, the distal tibial physis contributes approximately 5 mm of longitudinal growth per year [6]. Angular deformities and limb length discrepancies may manifest 1 to 2 years following a physeal injury [7].

There is evidence in the literature suggesting that factors such as the Salter-Harris (SH) classification of the fracture, the degree of initial displacement, the magnitude of the physeal gap following surgical intervention, the presence of an associated fibular fracture, and the timing of surgical treatment are significantly correlated with the risk of premature physeal closure [1,2,8]. It has been reported that Salter-Harris type I and II fractures, as well as achieving anatomic reduction, are associated with a reduced risk of premature physeal closure [5].

The literature includes multiple publications examining the relationship between Salter-Harris fracture types and premature physeal closure. However, no studies have comprehensively analyzed Triplane, McFarland, Tillaux, and other Salter-Harris fracture

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types together.

In this study, we aimed to evaluate the impact of initial post-reduction displacement, Salter-Harris (SH) fracture type, the method of reduction, the presence of an associated fibular fracture, and the mechanism of trauma on the occurrence of physeal arrest. Our hypothesis was that the risk of premature physeal closure increases with higher Salter-Harris classifications and greater injury energy.

2. Materials and Methods

This retrospective study was conducted following approval from the Local Ethics Committee (approval number: AEŞH-BADEK-2024-450). Two different centers were included in our study: Ankara Bilkent City Hospital between March 2019- March 2024 and Ankara Etlik City Hospital November 2022-March 2024 Orthopedics and Traumatology Clinic between March 2019-March 2024. The centers included in this study are designated advanced trauma centers, with comparable surgical equipment and a similar level of surgical expertise across all institutions. The study included patients who underwent surgery for pediatric distal tibial fractures involving physics. Patients who were postoperative for at least 6 months and had complete preoperative and postoperative radiological and clinical data were included in the study. Patients with open fractures, patients with pathological fractures, patients with fractures in more than one extremity, and patients who were followed conservatively with a cast were excluded from the study.

Data such as age, gender, affected side, fracture type (Salter-Harris classification, McFarland fracture, Tillaux ,Triplane fracture), amount of displacement after initial reduction, presence of fibula fracture, open or closed reduction, fixation method, mechanism of injury (falling, sports injury, traffic accident), Lateral Distal Tibial Angle (LDTA) and Anterior Distal Tibial Angle (ADTA) at last follow-up were extracted from the database.

Radiographic measurements were conducted using the Picture Archiving and Communication System (PACS). Radiological measurements were made by an experienced orthopedic surgeon. Angular deformity of the ankle was measured using a line drawn parallel to the tibial plafond and a second line drawn parallel to the tibial shaft based on AP and lateral radiographs (Figure 1) [9].

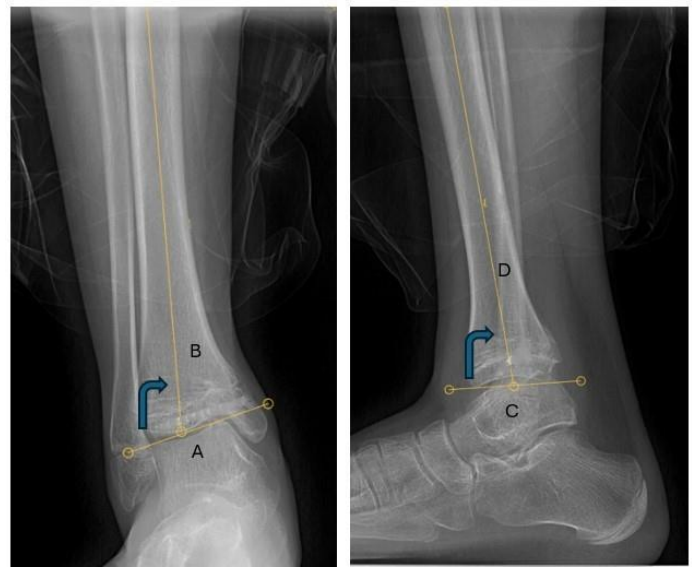
2.1. Statistical analysis

SPSS version 21.0 software (IBM Corp., Armonk, NY, USA) was utilized for statistical analysis. The normality of variable distributions was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as Q-Q plots and histograms. Variables with normal distributions were presented as mean ± standard deviation, while non-normally distributed variables were reported as median (minimum-maximum) values. Categorical data were expressed as frequency (percentage).

For comparisons, the Pearson Chi-square test was employed for categorical variables with sufficient observations, while Fisher's Exact test was used for those with insufficient observations. Post hoc analyses for statistically significant results involving more than two categories were conducted using the Bonferroni method. For continuous variables, Student's t-test was applied to compare two independent groups with normal distributions, whereas the Mann-Whitney U test was used for non-normally distributed variables. A p-value of <0.05 was considered statistically significant.

Figure 1

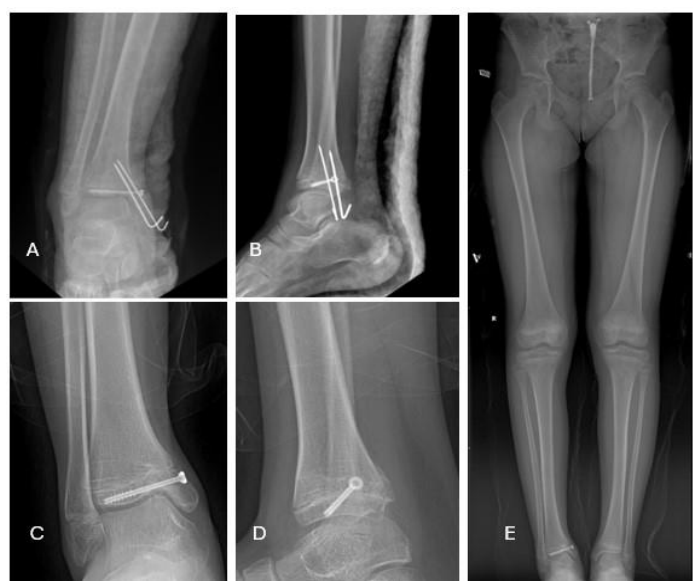
Measurement of angular deformity patients



A. Line drawn parallel to the tibial plafond on the anteroposterior radiograph, B. Line drawn along the tibial medullary axis on the anteroposterior radiograph, C. Line drawn parallel to the tibial plafond on the lateral radiograph, D. Line drawn along the tibial medullary axis on the lateral radiograph.

Figure 2

Postoperative radiographies



A. Early postoperative anteroposterior radiograph, B. Early postoperative lateral radiograph, C. 6th-month postoperative anteroposterior radiograph, D. 6th-month postoperative lateral radiograph, E. 6th-month postoperative limb length radiograph

3. Results

A total of 83 patients, comprising 59 males (71%) and 24 females (29%), were included in the study. The mean age of the patients was 12 years (8–15 years). Among the cases, 42 patients (50.7%) underwent surgery on the right side, while 41 patients (49.3%) had surgery on the left side.

Among the patients, 4 (4.8%) were diagnosed with McFarland fractures, 27 (32.5%) with Salter-Harris (SH) type 2 fractures, 15 (18%) with SH type 3 fractures, 6 (7.2%) with SH type 4 fractures, 8 (9.6%) with Tillaux fractures, and 23 (27.7%) with triplanar fractures (**Table 1**). During surgery, a closed reduction was performed in 70 patients (84.4%), while open reduction was performed in 13 patients (15.6%). Fixation methods included cannulated screws in 56 patients (64.7%), K-wires in 25 patients (30.1%), and a combination of both K-wires and cannulated screws in 2 patients (2.4%) (**Table 1**).

Premature physeal closure was observed in 10 patients (12%). Among six patients with SH type 4 fractures, three experienced physeal closure. Additionally, two out of four patients with McFarland fractures developed premature physeal closure, and one of these cases progressed to varus deformity. The patient with varus deformity underwent corrective osteotomy at the sixth month post-injury. Analysis of the mechanism of injury revealed that fractures resulting from traffic accidents were significantly associated with an increased incidence of premature physeal closure (**Table 2**).

It was determined that the amount of residual displacement after the initial reduction and the presence of an associated fibular fracture had no significant effect on the incidence of premature physeal closure (**Table 2**).

The mean lateral distal tibial angle (LDTA) and anterior distal tibial angle (ADTA) values for the patients were within normal limits, except for one patient. In a patient with a McFarland fracture, the LDTA was measured at 104°, indicating the presence of varus deformity (**Figure 2**). Notably, the ADTA values were found to be within normal limits in all patients, including the patient with varus deformity (**Table 3**).

Table 1

Summary of Patient Data for Patients

		n=83[1]
Gender	❖ Male	59 (71.0%)
	❖ Female	24 (29.0%)
Age (years)		12 (8-16)
Side	▪ L	41 (49.3%)
	▪ R	42 (50.7%)
Fracture Type	❖ McFarland	4 (4.8%)
	❖ SH-Type 2	27 (32.5%)
	❖ SH-Type 3	15 (18.0%)
	❖ SH-Type 4	6 (7.2%)
	❖ Tillaux	8 (9.6%)
	❖ Triplanar	23 (27.7%)
Surgery	▪ Cannulated Screw	56 (67.4%)
	▪ K-wire	25 (30.1%)
	▪ Both	2 (2.4%)
Post-Reduction Displacement (mm)		2.4 (1.0-9.2)
Physis closed	❖ Open	73 (88%)
	❖ Closed	10 (12%)
Reduction Methods	▪ Open	13(15.6%)
	▪ Closed	70 (84.4%)
Fibula Fracture	❖ Yes	14 (16.8%)
	❖ no	69 (83.1%)
Last Follow-up LDTA (degrees)		89 (88-104)
Last Follow-up ADTA		80 (78-84)
Injury Mechanism	▪ Fall	37 (44.5%)
	▪ Sports injury	36 (43.3%)
	▪ Traffic accident	10 (12%)

[1]*:n (%), median(min.-max.)*
ADTA: Anterior Distal Tibial Angle
LDTA: Lateral Distal Tibial Angle

Table 2

The data of patients between premature physeal closure group and open physis group

		Open Physis, N=73[1]	Premature Physeal Closure, N=10[1]	p
Gender	❖ Male	52 (71.2%)	7 (70%)	>0.999[2]
	❖ Female	21 (28.7%)	3 (30%)	
Age (years)		12 (8-15)	13 (9-15)	0.684[3]
Side	▪ Left	34 (46.5%)	7 (70%)	0.085[2]
	▪ Right	39 (53.5%)	3 (20%)	
Fracture Type	❖ McFarland	2 (2.7%)	2 (20%)	0.015[2]
	❖ SH type 2	26 (35.6%)	1 (10%)	
	❖ SH type 3	15(20.5%)	2 (20%)	
	❖ SH type 4	3 (4.1%)	3 (30%)	
	❖ Tillaux	7 (9.5%)	1(10%)	
	❖ Triplane	21 (28.7%)	1 (10%)	
Post-Reduction Displacement (mm)		2.4 (1.0-9.2)	2.5 (1.6-5.1)	0.619[3]
Reduction	▪ Open	8 (10.9%)	4 (40%)	0.054[2]
	▪ Close	65 (89.0%)	6 (60%)	
Fibula Fracture	❖ Yes	10 (13.6%)	4 (40%)	0.076[2]
	❖ No	63 (86.4%)	6 (60%)	
Last Follow-Up LDTA (degrees)		89 (88-90)	89 (88-104)	0.837[3]
Last Follow-Up ADTA (degrees)		80 (78-84)	82 (80-84)	0.107[3]
Trauma Mechanism	▪ Fall	36 (49.3%)	2 (20%)	0.015[2]
	▪ Sports injury	33 (45.2%)	4 (40%)	
	▪ Traffic accident	4 (5.4%)	4 (30%)	

[1]: n(%); Median (min.-max.), [2]: Fisher exact Test, [3]: Mann-Whitney U Test

Table 3

The data of patients in premature physeal closure group

No	Gender	Age (Years)	Side	Fracture Type	Surgery	Initially Displacement	Reduction Type	Fibula Fracture	Deformity	Last Follow-up LDTA (°)	Last Follow-up ADTA (°)	Trauma Mechanism
1	Male	14	L	Triplanar	Cannulated screw	2.5	Close	Yes	No	89	82	Fall
2	Female	10	L	McFarland	Cannulated screw	2.5	Open	No	No	91	84	Sports Injury
3	Male	14	L	Tillaux	Cannulated screw	4.8	Open	No	No	89	82	Fall
4	Male	13	R	SH Type 2	Cannulated screw	1.8	Close	No	No	89	81	Traffic Accident
5	Male	14	L	SH Type 3	Cannulated screw	2.2	Close	Yes	No	88	83	Sports Injury
6	Male	9	L	SH Type 3	K-wire	1.6	Close	No	No	89	80	Fall
7	Male	15	L	SH Type 4	Cannulated screw	5.1	Open	No	No	89	80	Sports Injury
8	Male	11	L	SH Type 4	Cannulated screw	3.5	Close	Yes	No	89	80	Traffic Accident
9	Male	13	R	SH Type 4	K-wire	2.4	Close	No	No	88	82	Sports Injury
10	Female	12	R	McFarland	K-wire and cannulated screw	2.2	Open	No	Yes	104	82	Traffic Accident

4. Discussion

The most significant finding of our study is that Salter-Harris type 4 fractures and McFarland fractures are associated with a significantly higher incidence of premature physeal arrest. Another key result is that injuries resulting from traffic accidents are more frequently associated with premature physeal arrest compared to those caused by simple falls or sports-related injuries.

Several risk factors contribute to premature physeal arrest following pediatric distal tibial physeal fractures, including the type of fracture, mechanism of injury, initial displacement, number of reduction attempts, quality of reduction, and patient age. In a study conducted by Rohmiller et al.[10], growth disturbances of the physis were observed in 39.6% of cases involving Salter-Harris (SH) type 1 and type 2 fractures. In a study conducted by Barmada et al., premature physeal arrest was most commonly observed in Salter-Harris (SH) type 3 and type 4 fractures. Additionally, SH type 1 and type 2 fractures were identified as the second most frequent types associated with physeal arrest [5]. In various studies, differing results have been reported due to the heterogeneity of study groups and a predominant focus on fracture classification rather than the mechanism of injury. Similarly, in our study, premature physeal arrest was most frequently observed in Salter-Harris (SH) type 4 fractures.

The fractures referred to as McFarland fractures, involving the medial malleolus, can be classified as Salter-Harris (SH) type 4 or type 5 fractures [8]. It has been reported that physeal bar formation can occur in up to 50% of McFarland fractures [1,8,11]. In a study conducted by Petratos et al.[8], the incidence of premature physeal arrest in McFarland fractures was reported to be 35%. In our study, both McFarland fractures were classified as SH type 4 fractures, and the observed physeal bar formation was consistent with the literature. Among all distal tibial fractures involving the physis in our study, only one McFarland fracture resulted in a varus deformity requiring surgical correction. This patient underwent corrective osteotomy at the sixth month post-injury.

In older pediatric populations, triplanar and Tillaux fractures are typically associated with a low risk of premature epiphyseal plate closure[5]. The literature reports a frequency of premature epiphyseal closure in triplanar fractures ranging between 4% and 21% [5,12]. In our study, the incidence of premature epiphyseal closure in triplanar fractures was found to be 4.5%, which is consistent with the reported range in the literature. Although premature physeal closure has not been reported in the literature following Tillaux fractures, in our study, physeal arrest was observed in 12.5% of Tillaux fractures [13]. This high rate is thought to be attributable to the small sample size in this group and the relatively lower average age of the patients.

Several studies have highlighted a significant association between the mechanism of injury and the occurrence of premature epiphyseal arrest. Rohmiller et al.[10] reported that pronation-abduction type injuries are more frequently linked to premature physeal arrest compared to supination-external rotation type injuries. Furthermore, it has been proposed that the energy magnitude of the trauma plays a significant role in determining the likelihood of premature physeal arrest[14]. Physeal arrest was observed more frequently in patients with fractures resulting from traffic accidents. We hypothesize that the likelihood of premature physeal arrest increases with the energy level of the trauma.

The retrospective nature of our study and the relatively small sample size represent its primary limitations. However, the inclusion of diverse fracture types, such as Salter-Harris, triplanar, McFarland, and Tillaux fractures, and the comparative analysis of these groups are considered valuable contributions to the existing literature. Nevertheless, further prospective, randomized studies are needed to provide more robust evidence on this topic.

5. Conclusion

High-energy trauma, Salter-Harris type 4 fractures, and McFarland fractures are significant risk factors for premature physeal arrest. In this context, it is crucial to inform the parents of the affected children about these risks and emphasize the importance of close follow-up in these cases to monitor for potential complications.

Statement of ethics

This study was approved by the Ethics Committee of Ankara Etlik City Hospital Ethics Committee (2024-450) The study was performed according to the Declaration of Helsinki.

Source of Finance

The authors declare that they have received no financial support for this study

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The data supporting the conclusion of this article will be available by the authors without undue reservation.

Author contributions

Concept: YE/ASN, Design: ASN/ŞG/TT, Literature search: YE/EV/EA/TT, Data Collection and Processing: ASN/ŞG/EA, Analysis or Interpretation: TT/EV/ŞG, Writing: YE/ASN/EV

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Clinical Correlates of Non-Motor Symptoms and Quality of Life in Parkinson's Disease Patients: Analysis of Motor and Non-Motor Features

Miray Erdem[1], Derya Özdoğru[1]

1 Department of Neurology, University of Health Sciences, Adana City Training and Research Hospital, Adana, Türkiye

Abstract

Aim: Non-motor symptoms (NMS) significantly impact Parkinson's disease (PD) patients, yet their relationship with disease progression and quality of life requires further investigation. We aimed to evaluate the relationships between NMS burden, motor symptoms, disease duration and quality of life in PD patients.

Methods: In our study, 141 patients (60 females, 81 males; mean age 63.0 (33.0 - 93.0)) with PD diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria for Idiopathic PD were included. NMS were assessed using the NMS Scale. Motor symptoms were evaluated using Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Hoehn-Yahr (H&Y) staging. Quality of life was measured using Parkinson's Disease Questionnaire-39 (PDQ-39). Disease duration was categorized into three groups: <4 years, 5-8 years, and >9 years. Statistical analyses included correlation coefficients, multivariate logistic regression, and linear regression models.

Results: NMS burden strongly correlated with quality of life (r=0.507, p<0.001) and motor symptoms (r=0.504, p<0.001). Age (p<0.001), disease duration 5-8 years (p<0.001) or 9< years (p<0.001), UPDRS-III (p<0.001), levodopa equivalent daily dose (LEDD) (p<0.001) and H&Y >3 (p<0.001) were significant in the univariate analysis. In the multivariate stage, age (p<0.001), disease duration 9< years (p=0.015) and UPDRS-III (p=0.004) remained statistically significant. Each one-unit increase in UPDRS-III increased PDQ-39 by 1.91 points and each one-point increase in NMS total score increased PDQ-39 by 3.35 points (p<0.001 for each).

Conclusion: Our study once again emphasizes the importance of non-motor symptoms in PD. Instead of the traditional approach focusing on motor symptoms, approaches that will address the quality of life of patients in a holistic manner should be developed.

***Keywords**: Parkinson's Disease, Non-Motor Symptoms, Quality of Life, Disease Progression, Movement Disorders*

1. Introduction

Parkinson's disease (PD) is a multisystem disorder associated with α-synuclein aggregates throughout the central, autonomic and peripheral nervous system, clinically characterized by motor and non-motor symptoms (NMS)[1]. Current criteria define PD as the presence of resting tremor, rigidity or bradykinesia with both. However, the clinical presentation is multifaceted and includes many non-motor symptoms[1].

Representing a preclinical phase spanning 20 or more years, NMS in PD is linked to the widespread distribution of α-synuclein pathology that is not restricted to the dopaminergic nigrostriatal system, which is responsible for the core motor features of PD[2]. There is increasing evidence that mitochondrial dysfunction, microglial activation, α-synuclein accumulation, ageing and protein misfolding contribute to the development of Parkinson's disease (PD). In addition, neuroinflammation, oxidative stress and impaired antioxidant defenses play an important role in its pathogenesis[3]. In addition to the non-nigral brainstem nuclei, α-synuclein pathology involves the sympathetic and parasympathetic, enteric, cardiac and pelvic plexuses, and many other organs, showing a topographic and chronological spread, especially in the prodromal stages of the disease[2]. In this context, symptoms such as olfactory disturbance, constipation, cardiovascular dysfunction, rapid eye movement (REM) sleep behavior disorder, depression, anxiety and others have been described[4-6]. Despite the studies, the pathophysiological mechanisms underlying NMS remain unclear and both dopaminergic (DA) and non-DA systems are thought to play a role[2]. However, it is a known fact that the severity and burden of NMS increase over time, impairing the quality of life of patients,

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increasing the burden of caregivers and social costs[7,8]. Therefore, it is very important to understand that non-motor symptoms should be addressed together with motor symptoms for the proper care of PD patients.

In our study, we aimed to evaluate the relationships between NMS burden and subscale scores and motor symptoms, disease duration, levodopa equivalent daily dose (LEDD) and quality of life in PD patients.

2. Materials and Methods

2.1. Design of study and compliance

In our cross-sectional study conducted in strict adherence to the Declaration of Helsinki, the study protocol was approved by the local Ethics Committee in Adana, Turkey, at its meeting on 05 December 2024 (decision no: 250) and written informed consent was given by all participants. Informed consent complies with standards for scientific studies and includes a detailed and understandable summary of the study, the purpose of the study, confidentiality criteria, times and methods of preservation of biological material, and personal information of the participants.

2.2 Study participants

In our study, 141 patients (60 females, 81 males; mean age 63.0 (33.0 - 93.0)) with PD diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank Criteria for Idiopathic PD were included. Patients were divided into three groups according to disease duration: <4 years, 5-8 years and >9 years. Patients with Parkinson plus syndrome, those with secondary parkinsonism (drug-induced, vascular, tumoral causes), those with a previous diagnosis of dementia or psychosis, and those who could not cooperate with the tests were excluded. In addition to a detailed history and neurological examination performed by the same movement disorder specialist, demographic findings and treatments were recorded and non-motor symptoms were recorded with the NMS scale. The NMS scale[9] consists of 30 questions with a dichotomous response of present or absent for each item in six domains: neuropsychiatric symptoms (items 12-17, 30), autonomic disorders (items 1, 3-9, 18-21, 28), olfactory disorders (item 2), sleep disorders (items 22-26), sensory symptoms (item 10) and the others (items 11, 27, 29). The total NMS scale score ranges from 0-30 by counting "yes" responses. The scores indicate how many different NMS the patient has. Accordingly, patients were classified as mild (1-5 points), moderate (6-9 points), severe (10-13 points) and very severe (≥14 points). Unified Parkinson's Disease Rating Scale (UPDRS) motor scores[10] Hoehn-Yahr (H&Y) stage[10,11] and LEDD were recorded. In addition, quality of life was evaluated with the Parkinson's Disease Questionnaire – 39 (PDQ-39)[12] scale.

2.3. Statistical Method

Statistical analyses were performed using Jamovi (Version 2.3.28) and JASP (Version 0.19.2) software packages. In the analysis of demographic and clinical characteristics of Parkinson's patients, the conformity of continuous variables to normal distribution was evaluated by Shapiro-Wilk test and Q-Q plot graphs. Since the data were not normally distributed, descriptive statistics of numerical data were presented as median [minimum-maximum] and categorical data were presented as frequency (n) and percentage (%).

Kruskal-Wallis H test for continuous variables was used to compare the clinical characteristics and NMS severity of the patients according to disease duration (<4 years, 5-8 years, 9< years). When significant differences were found between the groups, post-hoc pairwise comparisons were performed with the Dwass-Steel-Critchlow-Fligner test. Pearson Chi-square test or Fisher's Exact/Fisher Freeman Halton test was used for the comparison of categorical variables (gender, educational status, H&Y scale, NMS severity classification) between the disease duration groups when the expected values were less than 5.

Spearman correlation analysis was used to analyse the relationships between the total NMS scale score, subscale scores and other clinical parameters (age, duration of education, PDQ-39, UPDRS-III, LEDD) because the variables were not normally distributed. Correlation coefficients (r) were calculated and significance levels were determined.

Univariate and multivariate logistic regression analyses were performed to determine the determinants of H&Y scale score (≤2 and >3). Model fit was analyzed by Hosmer-Lemeshow test ($p>0.05$). Variance inflation factors (VIF<10) and tolerance values (>0.2) were calculated for the multicollinearity problem between independent variables. The linearity assumption was checked by evaluating the relationship between the continuous independent variables and the logit transformed dependent variable with the Box-Tidwell test. Standardized residuals (±3), Cook's distance (<1) and leverage values were examined for outliers and influential observations. In univariate analyses, the effects of age, gender, educational status, disease duration, UPDRS-III, LEDD and NMS total score were examined. Variables with $p<0.20$ in univariate analyses were included in the multivariate model, while clinical importance was also considered in variable selection. Results were presented with odds ratio (OR) and 95% confidence intervals.

Linear regression analyses were performed separately to determine the factors affecting PDQ-39 quality of life scale, UPDRS-III motor symptom score, LEDD and NMS total score. Univariate analyses were performed for each dependent variable. In multivariate models, enter method was used and variables with $p<0.20$ in univariate analyses were evaluated. Regression coefficients (β) and 95% confidence intervals were calculated. Assumptions (normality, linearity, equivariance, multicollinearity, multicollinearity) were checked for the suitability of the models.
The significance level was accepted as $p\leq0.05$ in all statistical analyses. In post-hoc analyses for inter-group comparisons, p values corrected for multiple comparisons were used.

3. Results

The median age of the PD (n=141) who participated in the study was 63 years (33-93), 57.4% were male (n=81) and 42.6% (n=60) female. Formal education was available in 76.6% of the patients and the median duration of education was 5 years (3-15). The median disease duration was 1 year (1-3), PDQ-39 quality of life scale score was 51 (4-134), UPDRS-III motor symptom score was 16 (6-40) and LEDD was 400 mg/g (150-1700). 72.3% (n=102) of the patients had H&Y stage ≤2. According to the total score of the NMS scale, 22% of the patients had mild (1-5 points), 27% moderate (6-9 points), 25.5% severe (10-13 points) and 25.5% very severe (≥14 points) non-motor symptoms (**Table 1**).

Significant positive correlations were found between NMS scale total score and age (r=0.380), PDQ-39 (r=0.507), UPDRS-III (r=0.504) and LEDD (r=0.473) ($p<0.001$ for all). When the subscales were analysed, gastrointestinal symptoms correlated with LEDD (r=0.352, $p<0.001$) and UPDRS-III (r=0.248, p=0.003); urinary symptoms correlated with age (r=0.431, $p<0.001$) and LEDD (r=0.381, $p<0.001$); sexual dysfunction with UPDRS-III (r=0.353, $p<0.001$) and age (r=0.290, $p<0.001$); cardiovascular/falling symptoms with UPDRS-III (r=0.480, $p<0.001$) and PDQ-39 (r=0.282, $p<0.001$); attention/memory problems with PDQ-39 (r=0.411,

p<0.001) and age (r=0.272, p=0.001); sleep disorders showed significant correlations with PDQ-39 (r=0.414, p<0.001) and UPDRS-III (r=0.323, p<0.001) (**Table 2**).

Linear regression analyses for the PDQ-39 score showed a higher score of 27.25 points (p<0.001) in patients with a disease duration of 5-8 years and 13.43 points (p=0.029) in patients with a disease duration of 9< years compared to the <4 year group. Each one-unit increase in UPDRS-III increased PDQ-39 by 1.91 points and each one-point increase in NMS total score increased PDQ-39 by 3.35 points (p<0.001 for each). In multivariate analysis, UPDRS-III (p<0.001) and NMS total score (p<0.001) remained significant, whereas the significance of disease duration and LEDD variables disappeared (**Table 3**).

Age (p<0.001), disease duration 5-8 years (p<0.001) or 9< years (p<0.001), UPDRS-III (p<0.001), LEDD (p<0.001) and H&Y >3 (p<0.001) were significant in the univariate analysis. In the multivariate stage, age (p<0.001), disease duration 9< years (p=0.015) and UPDRS-III (p=0.004) remained statistically significant; the effects of LEDD and H&Y were not significant at this level (p>0.05) (**Table 4**). These results showed that the progressive increase of both motor and non-motor symptoms in PD was associated with prolonged disease duration and an increase in UPDRS-III score, whereas quality of life was more under the integrated effect of motor and non-motor burden.

Table 1

Descriptive statistics on demographic and clinical characteristics in patients with Parkinson's disease

		Overall (n=141)
Age		63.0 [33.0 - 93.0]
Gender (%)	Woman	60 (42.6)
	Male	81 (57.4)
Education Status (%)	None	33 (23.4)
	There is	108 (76.6)
Duration of Education (year)		5.0 [3.0 - 15.0]
Duration of Illness		1.0 [1.0 - 3.0]
PDQ-39		51.0 [4.0 - 134.0]
H&Y Scale (%)	≤ 2	102 (72.3)
	>3	39 (27.7)
UPDRS-III		16.0 [6.0 - 40.0]
LEDD		400.0 [150.0 - 1700.0]
NMS Scale Total Score Classification	Light (1-5)	31 (22.0)
	Medium (6-9)	38 (27.0)
	Heavy (10-13)	36 (25.5)
	Very severe (≥14)	36 (25.5)
NMS Scale Total Score		10.0 [2.0 - 17.0]
Gastrointestinal		2.0 [0.0 - 5.0]
Urinary		2.0 [0.0 - 2.0]
Sexual function		0.0 [0.0 - 2.0]
Cardiovascular/Fall		0.0 [0.0 - 2.0]
Attention/Memory		1.0 [0.0 - 3.0]
Perception problems		0.0 [0.0 - 2.0]
Mood		1.0 [0.0 - 2.0]
Sleep		1.0 [0.0 - 4.0]
Other		1.0 [0.0 - 3.0]

‡: n (%), §: Median [Min.-Max.], H&Y Scale: Hoehn-Yahr Scale, LEDD: Levodopa Equivalent Daily Dose, NMS: Non-Motor Symptom, PDQ-39: Parkinson's Disease Questionnaire-39, UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

Table 2

Correlation of demographic and clinical characteristics with non-motor symptom severity in patients with Parkinson's disease

	Age		Training Duration		PDQ-39		UPDRS-III		LEED	
	r	p	r	p	r	p	r	p	r	p
NMS Scale Total Score	0.380	<0.001	-0.054	0.580	0.507	<0.001	0.504	<0.001	0.473	<0.001
Gastrointestinal	0.171	0.042	0.023	0.815	0.188	0.026	0.248	0.003	0.352	<0.001
Urinary	0.431	<0.001	-0.255	0.008	0.138	0.102	0.222	0.008	0.381	<0.001
Sexual function	0.290	<0.001	0.056	0.564	0.180	0.033	0.353	<0.001	0.261	0.002
Cardiovascular/Fall	0.240	0.004	-0.131	0.178	0.282	<0.001	0.480	<0.001	0.205	0.015
Attention/Memory	0.272	0.001	-0.108	0.267	0.411	<0.001	0.243	0.004	0.210	0.012
Perception problems	-0.051	0.545	0.178	0.066	0.134	0.114	-0.013	0.875	0.123	0.145
Mood	0.067	0.432	0.153	0.115	0.370	<0.001	0.152	0.072	0.181	0.031
Sleep	0.222	0.008	-0.132	0.172	0.414	<0.001	0.323	<0.001	0.300	<0.001
Other	0.093	0.275	0.047	0.632	0.293	<0.001	0.310	<0.001	0.230	0.006

Spearman's rho correlation coefficient was used., Notes: Bold p-values indicate statistical significance (p≤0.05).
LEDD: Levodopa Equivalent Daily Dose, NMS: Non-Motor Symptoms, PDQ-39: Parkinson's Disease Questionnaire-39, UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

Table 3

Linear regression analysis results for factors affecting quality of life in patients with Parkinson's disease

Linear regression predicting PDQ-39	Univariate Linear Regression		Multivariate Linear Regression	
	β [95% CI]	p	β [95% CI]	p
Age	0.18 [-0.35 - 0.71]	0.510	-	-
Gender Man vs. Female	4.16 [-6.71 - 15.04]	0.454	-	-
Education Status: Yes vs. No	-3.51 [-16.22 - 9.2]	0.589	-	-
Disease Duration: ref.=<4 years				
5-8 years	27.25 [12.29 - 42.2]	<0.001	9.38 [-6.57 - 25.32]	0.251
9< year	13.43 [1.53 - 25.33]	0.029	-1.7 [-15.42 - 12.02]	0.808
UPDRS-III	1.91 [1.37 - 2.44]	<0.001	1.52 [0.91 - 2.14]	<0.001
LEDD	0.02 [0.01 - 0.03]	0.007	-0.01 [-0.03 - 0.01]	0.257
NMS Scale Total Score	3.35 [2.24 - 4.46]	<0.001	2.3 [1.09 - 3.5]	<0.001

β: Unstandardised regression coefficient, CI: Confidence interval, LEDD: Levodopa Equivalent Daily Dose, NMS: Non-Motor Symptoms, PDQ-39: Parkinson's Disease Questionnaire-39, UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

Table 4

Linear regression analysis results for the factors affecting NMS total scores in patients with Parkinson's disease

Linear regression predicting NMS Score	Univariate Linear Regression		Multivariate Linear Regression	
	β [95% CI]	p	β [95% CI]	p
Age	0.17 [0.11 - 0.24]	<0.001	0.16 [0.1 - 0.21]	<0.001
Gender Man vs. Female	-0.82 [-2.27 - 0.63]	0.270	-	-
Education Status: Yes vs. No	-0.51 [-2.21 - 1.19]	0.555	-	-
Disease Duration: ref.=<4 years				
5-8 years	3.83 [1.94 - 5.71]	<0.001	1.66 [-0.37 - 3.68]	0.111
9< year	3.93 [2.43 - 5.43]	<0.001	2.2 [0.45 - 3.96]	0.015
UPDRS-III	0.22 [0.14 - 0.29]	<0.001	0.17 [0.06 - 0.28]	0.004
LEDD	0.01 [0.01 - 0.02]	<0.001	0.01 [0.01 - 0.02]	0.060
H&Y Scale: >3 vs. ≤ 2	3.14 [1.62 - 4.67]	<0.001	-1.37 [-3.54 - 0.8]	0.218

β: Unstandardised regression coefficient, CI: Confidence interval, H&Y Scale: Hoehn-Yahr Scale, NMS: Non-motor symptom scale, LEDD: Levodopa Equivalent Daily Dose, UPDRS-III: Unified Parkinson's Disease Rating Scale Part III.

4. Discussion

The most Although NMS manifestations of PD are less noticeable than motor symptoms, they have a critical impact on quality of life during the disease process. In our study, the effect of NMS on quality of life and its relationship with disease duration, motor symptom severity and the total dose of dopaminergic treatment received by the patient were analyzed. The findings suggest that NMS is an important determinant of quality of life in PD and these symptoms become more prominent with disease progression.

In our study, significant positive correlations were found between NMS total score and age, UPDRS-III, PDQ-39 and LEDD. These findings confirm that the burden of NMS increases with increasing age and motor symptom severity, thus confirming the effect of disease progression on NMS. Focusing on the subparameters of NMSs, gastrointestinal, urinary and cardiovascular symptoms were found to reflect this relationship more strongly. For example, each one unit increase in NMS total score was associated with a significant increase in LEDD dose, suggesting that NMS may also influence dopaminergic treatment requirements.

The existing literature shows that NMS profoundly affects not only quality of life but also disease management in PD. Chaudhuri et al.[13] reported that NMS is common even in the early stages of PD and that these symptoms become more severe in the later stages. Our study also supports these findings; especially the fact that NMS total scores were significantly higher in patients with age and H&Y score >3 suggests that these symptoms constitute a burden that cannot be ignored at every stage of the disease. Furthermore, the strong correlation between PDQ-39 and NMS total score is consistent with the literature emphasizing the impact of NMS on quality of life[14].

When the subparameters of NMS were analyzed, it was observed that gastrointestinal, urinary and sexual function symptoms increased remarkably. In Cankaya's study, the effect of these symptoms on patients' activities of daily living was emphasised[15]. However, our study also draws attention to the relationship between these symptoms and LEDD and reveals that high dose levodopa treatment alleviates some symptoms and exacerbates others. The effect of LEDD on NMS is discussed in the literature. Pekel et al. reported that high dose treatment had a favorable effect especially on gastrointestinal symptoms[16]. However, in our study, this effect was found to differ according to individual NMS types.

The limitations of our study include the limited number of participants and the lack of long-term follow-up data. In addition, it is thought that a more detailed analysis on the effects of NMS in different age groups should be performed. However, our findings have important implications for clinical management. It is clear that NMS should be addressed not only in the advanced stages of PD but also in the early stages and should be treated with a multidisciplinary approach. In our study, in which the effects of follow-up and early recognition of non-motor symptoms as well as motor symptoms of Parkinson's disease on quality of life were clearly demonstrated, it is thought that quality of life is an important criterion for managing

the treatment strategies of patients and intervening at the right time.

For future studies, it is recommended to investigate in more depth how NMS change in different disease stages, the mechanisms of their relationship with LEDD, and the effects of these symptoms at the individual level. Identification of latent structures between NMS subparameters by advanced statistical methods such as structural equation modelling may help us to better understand the effects of these symptoms on quality of life in PD.

5. Conclusion

Our study once again emphasizes the importance of non-motor symptoms in PD. Instead of the traditional approach focusing on motor symptoms, approaches that will address the quality of life of patients in a holistic manner should be developed.

Statement of ethics

Ethical approval was obtained from the Adana City Training and Research Hospital Ethics Committee and the study was conducted by the principles of the Declaration of Helsinki (05/12/24, no:250). Informed consent forms were obtained from all patients and control subjects.

Author Contributions

Concept: ME/DO, Design: ME/DO, Literature search: ME, Data Collection and Processing: ME/DO, Analysis or Interpretation: ME/DO, Writing: ME/DO.

Source of Finance

The authors declare that they have received no financial support for this study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Comparison of Percutaneous Screw Fixation and Conservative Treatment of Posterior Malleolar Fractures: A Radiological and Functional Outcomes Analysis

Mehmet Maden*[1], Tayfun Bacaksız[2], İhsan Akan [2], Özgür Doğan Aydın[3], Cem Özcan[2]

1 Department of Orthopedics and Traumatology, Izmir Atatürk Training and Research Hospital, Izmir, Türkiye
2 Department of Orthopedics and Traumatology, Izmir Katip Celebi University, Izmir, Türkiye
3 Department of Orthopedics and Traumatology, Izmir City Hospital, Izmir, Türkiye

Abstract

Aim: The aim of this study was to compare the clinical and radiological results in patients with trimalleolar fractures with a small posterior malleolar fragment of the ankle joint with and without percutaneous screw fixation.

Methods: The study involved patients (18-65 years) with (Group 1) or without (Group 2) percutaneous screw fixation of posterior malleolus fractures between January 2017 and December 2023. Clinical and radiological evaluation was conducted at various time points up to the last follow-up. Functional evaluation was conducted using American Orthopedic Foot and Ankle Scores (AOFAS), Visual Analogue Scores (VAS), and dorsiflexion restriction. Radiological evaluation included the measurement of the gap and step between at the fracture site and presence of ankle osteoarthritis.

Results: In this study, sixty-five patients (Group 1: 33, Group 2: 32) who met the inclusion criteria were followed up for a mean of 31.65±6.4 (24–44) months. There were no significant differences in the clinical results between the groups ($p > 0.05$). At the final radiograph, the mean gap and step distances in Group 1 were lower than in Group 2 ($p < 0.001$). There was no significant difference between the groups regarding the presence of ankle osteoarthrosis ($p = 0.658$).

Conclusion: This study indicates that while percutaneous screw fixation of small posterior malleolus fragments does not significantly improve clinical outcomes compared to non-fixation, it does result in better radiological alignment. The findings suggest that maintaining joint congruity may be more crucial than fixation in preventing posttraumatic ankle osteoarthritis. Further research is needed to explore these findings.

Keywords: *Posterior malleolus; Fracture; Screw fixation; Conservative*

1. Introduction

The posterior malleolus is crucial for the ankle joint, providing tibiotalar load transfer, rotational stability, and posterior talar support because it covers the load-bearing portion of the tibial plafond and the ankle syndesmosis. Posterior malleolus (PM) fractures account for approximately 7-44% of all ankle fractures and are usually associated with other malleolus fractures and syndesmosis injury leading to instability[1,2]. The Haraguchi classification is one of the most widely used classifications of posterior malleolus fractures[3]. Haraguchi Type 1 is a triangular fragment type involving the posterolateral corner of the tibial plafond and accounts for approximately 67% of all PM fractures[4,5]. If these fractures involve more than 25% of the articular surface, they should be fixed to provide greater syndesmotic stability[6]. Percutaneous screws are a safe and minimally invasive method frequently used for PM fragment fixation. Although surgical treatment is recommended for large posterior malleolus fractures, there is no consensus in the literature regarding the fixation of PM fragments less than 25% of the ankle joint and there are studies showing that conservative treatment is also effective [7,8].

In our study, we aimed to compare the clinical and radiological outcomes of patients with trimalleolar fractures involving less than 25% of the ankle joint in Haraguchi Type 1 PM fractures, with and without percutaneous screw fixation.

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2. Materials and Methods

After ethics committee approval, patients who underwent trimalleolar fracture surgery in our hospital were retrospectively analyzed (Health Research Institutional Review Board IRB Number: 0066, Date: 18/07/2024). All patients signed informed consent form. In this study, patients whose posterior malleolus fractures were fixed with percutaneous screws (Group 1) or not (Group 2) between January 2017 and December 2023 were evaluated. This study included patients diagnosed with trimalleolar fractures between the ages of 18 and 65 who had PM fractures (<25% of tibia plafond) treated with screws or conservative management. The included patients also had preoperative and postoperative computer tomography (CT), underwent medial and lateral malleolar fracture fixation, and had at least 2 years of follow-up.

The present study excluded patients with open fractures, pathologic fractures, isolated posterior malleolus fracture, PM fragments fixed with plate screws, prior ankle complaints or surgical procedures, ipsilateral injury, fracture history in the same ankle, perioperative syndesmotic instability (positive cotton test) or performing syndesmotic stabilization, inappropriate x-rays, and follow-up for less than 2 years.

2.1. Surgical Technique

Surgical procedures were performed by the same specialized surgical team. All patients were operated under anesthesia in the supine position using a tourniquet. The affected ankle was sterilized and draped for surgery. First, the fibula fracture was fixed with plates and screws through a posterolateral incision. Then, through a separate incision, the medial malleolus fracture was fixed with cannulated screws. Treatment of the PM fragment was determined according to the surgeon's preference.

After fixation of the fibula and medial malleolus fractures, reduction of the posterior malleolus was achieved with ligamentotaxis in Group 1. After the reduction was controlled under fluoroscopy, fixation was performed using one or two cannulated screws through a percutaneous mini-incision over the anterior ankle joint. In Group 2, no fixation method was applied for the posterior malleolus fracture (Figure 1).

Following fracture fixation and skin closure, a plaster cast was applied to all patients postoperatively and an active range of motion exercises were started one month after surgery. Full weight bearing was allowed 3 months after surgery.

2.2. Clinical and Radiological Evaluations

Patients were followed up clinically and radiologically at regular intervals for a minimum of 2 years. The demographic data (age, gender, affected side, etc.) of all patients were recorded (Table 1).

Clinical assessment was performed using American Orthopedic Foot and Ankle Scores (AOFAS), Visual Analogue Scores (VAS), and dorsiflexion restriction (more than 10%) at the last follow-up. Clinical results were then compared between the groups.

Radiological evaluation was performed by a senior radiologist and orthopedic surgeon. A consensus was reached to make a final assessment if there was a disagreement between the surgeon and the radiologist. The classification of PM fracture was classified according to the Haraguchi system by examining ankle views and computed tomography [3]. The length of the PM fracture and tibia plafond measurements were conducted from preoperative lateral x-rays. The gap or step between the PM fragment and tibia plafond was evaluated and measured in millimeters using PACS software at the last follow-up. The presence of ankle osteoarthritis was also assessed on radiographs according to the previous study [9]. Radiological results were then compared between the groups.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS version 25.0. The relationship between non-parametric categorical data of the patients was analyzed using Pearson's chi-square test. The relationship between parametric numerical variables was analyzed using Student's t-test. Significance level was defined as $P < 0.05$.

3. Results

Sixty-five patients (Group 1:33, Group 2:32) were followed up for a mean of 31.65±6.4 (24–44) months. The mean age of the patients was 41.1±13.6 (21–63) years. There were 31 (47.7%) male and 34 (52.3%) female patients. In 18 cases (27.7%) traffic accidents, in 19 cases (29.2%) ankle sprain injuries and in 28 cases (43.1%) falls were recorded. The affected extremities were 30 (46.1%) right-sided and 35 (53.9%) left-sided. The mean time from injury to surgery was 3.3±1.1 (2–5) days. No significant difference was found between the two groups in terms of these demographic parameters ($p > 0.05$) (**Table 1**).

Figure 1

Radiographic images of patients with (bottom row) and without (top row) fixation of posterior malleolus fracture: preoperative anteroposterior (a,f) and lateral (b,g) ankle x-rays, computed tomography views (c,h), and postoperative anteroposterior (d,i) and lateral (e,i) ankle x-rays.

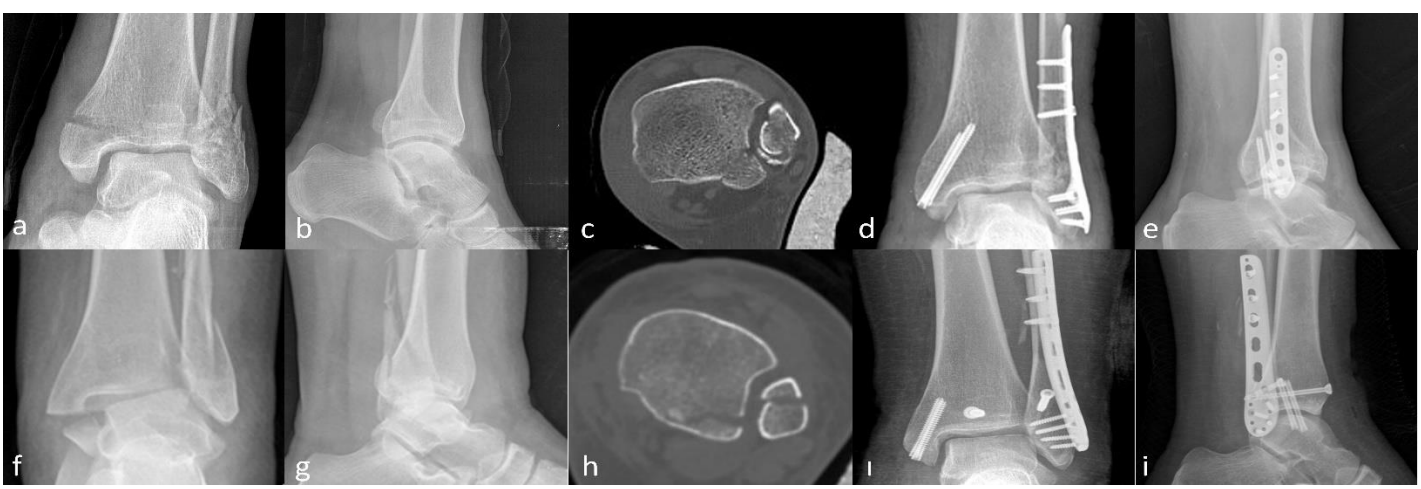

Table 1

Characteristics of the study population.

Variable	Group 1 Posterior malleol fixation (n=33)	Group 2 Posterior malleol without fixation (n=32)	p
Age (years)	41.5±14.6	40.6±12.6	0.787 +
Sex (male: female, n)	17:16	14:18	0.531 *
Affected side (right: left, n)	16:17	14:18	0.692 *
Mechanism of injury (fall: road accident: sprain, n)	11:7:15	9:9:14	0.791 *
Injury to surgery time (days)	3.4±1.1	3.3±0.9	0.839 +
Follow-up (month)	30.8±5.3	32.4±7.3	0.331 +

*+: Student t-test, *: Pearson Chi Square and Fisher's Exact test*

Table 2

Clinical results of two groups

Variable	Group 1 Posterior malleol fixation (n=33)	Group 2 Posterior malleol without fixation (n=32)	p
AOFAS Score (0: poor, 100: excellent)	91.2±5.8 (84-100)	93.3±4.9 (85-100)	0.130 +
VAS Score (0: no pain, 10: maximum pain)	1.27±1.1 (0-3)	1.13±0.9 (0-3)	0.537 +
>10% Dorsiflexion restriction	3 (9.1%)	2 (6.3%)	0.667 *

*AOFAS: The American Orthopedic Foot and Ankle Society, VAS: The Visual Analogue Scale, +: Student t-test, *: Pearson Chi Square and Fisher's Exact test*

Table 3

Radiological results of two groups.

Variable	Group 1 Posterior malleol fixation (n=33)	Group 2 Posterior malleol without fixation (n=32)	p
Gap (mm)	0.36±0.5 (0-2)	1.81±0.6 (1-3)	<0.001 +
Step (mm)	0.79±0.9 (0-3)	1.91±0.6 (1-3)	<0.001 +
Ankle osteoarthritis (n) (%)	3 (9.1%)	4 (12.5%)	0.658 *

*SD: Standard deviation, mm: millimeter, +: Student t-test, *: Pearson Chi Square and Fisher's Exact test*

At the last follow-up, the mean AOFAS and VAS scores were 92.2±5.5 (84-100) points and 1.2±0.9 (0-3) points for two groups. A loss of 10% or more dorsiflexion was found in 3 patients (9.1%) in Group 1, in 2 patients (6.3%) in Group 2. There were no significant differences in the clinical results between the groups ($p > 0.05$) (**Table 2**).

The mean gap distance between the posterior malleolus and tibia plafond was 1.1±0.9 (0-3) mm for all patients, and there was a significant difference among the groups. At the last x-rays, the mean gap distance in Group 1 [0.36±0.5 (0-2) mm] was lower than in Group 2 [1.81±0.6 (1-3) mm] ($p < 0.001$) (**Table 3**).

The mean step measurement between the posterior malleolus and tibia plafond was 1.3±0.9 (0-3) mm for all patients, and there was a significant difference among the groups. At the last x-rays, the mean step measurement in Group 1 [0.79±0.9 (0-3) mm] was lower than in Group 2 [1.91±0.6 (1-3) mm] ($p < 0.001$) (**Table 3**).

Ankle osteoarthritis was observed in only 7 (10%) of all patients. Early-stage arthritis was observed in 3 (9.1%) patients in Group 1 and 4 (12.5%) patients in Group 2. No significant difference was found between the groups in terms of ankle osteoarthritis ($p = 0.658$) (**Table 3**). All patients with ankle osteoarthritis presented a gap or step of more than 2 mm at the posterior malleolus fracture line. Any patients suffered from severe osteoarthritic changes.

4. Discussion

In the present study, we found that in patients with Haraguchi type 1 posterior malleolus fractures involving less than 25% of the ankle joint, there was less gap and step between the fractures when

the PM fragment was fixed with cannulated screws percutaneously. Although PM fixation resulted in better radiological alignment, clinical outcomes remained comparable to conservative treatment.

Fixation of the posterior malleol in trimalleolar fractures is determined according to the ratio of the posterior fragment to the ankle joint. There is a consensus in the literature about posterior fragment fixation for PM fragment size greater than 25% [4,10]. However, there are different studies suggesting operative or conservative treatment for PM fractures less than 25% of the ankle joint. Gardner et al. [6] recommended fixation to maintain syndesmotic stability even if the posterior malleolus fracture was less than 25%. However, Van Hooff et al. [7] showed that joint biomechanics did not change and functional results were similar with conservative treatment of small posterior malleolus fractures. Also, McDaniel and Wilson [11] concluded that failure of fixation of a posterior malleolus fragment measuring ≤25% would not affect the overall outcome. In our study, although better reduction quality was achieved in patients with PM fractures less than size of 25% of the distal tibial articular surface fixed with percutaneous screws compared to conservative treatment, no significant differences were found between the groups in terms of clinical outcomes, similar to previous studies [7,11].

Posterior malleolus fixation can be performed using screw or plate osteosynthesis via a posterolateral approach or an anteroposterior percutaneous screw technique. Anteroposterior or posteroanterior screw methods are frequently used because they are minimally invasive, less soft tissue dissection and lower risk of infection. Batar and Sisman [12] reported better clinical and radiological results with the posteroanterior screw technique compared to anteroposterior screw fixation due to direct reduction. On the other hand, Xu et al. [13] reported in a retrospective study that anatomical reduction was achieved similarly in patients with both posteroanterior and anteroposterior screw fixation. Although different fixation methods for posterior malleolus fixation were not compared in our study, we have shown that anteroposterior screw fixation provides less gap and step distance between fragments, is a reliable method to maintain reduction and results in good functional scores.

Posttraumatic ankle osteoarthritis is a progressive, degenerative articular cartilage disease that can occur after primary or neglected ankle fractures [14,15]. Ankle fractures involving the PM are associated with an increased incidence of posttraumatic osteoarthritis [16]. Especially the presence of fracture dislocation, joint surface incongruity and residual talar subluxation are risk factors for the development of posttraumatic ankle osteoarthritis, regardless of the size of the posterior malleolus fragment [4]. Therefore, some authors suggest that all posterior malleolus fractures should be fixed to decrease the incidence of ankle arthritis [1]. On the other hand, there are also studies showing that osteoarthritis develops more when the posterior malleolus fracture is surgically treated [4]. In the present study, it was observed that all patients with ankle osteoarthritis had a gap or step of more than 2 mm in the posterior malleolus. In our opinion, in order to prevent ankle arthritis, reduction and joint congruity should be maintained rather than fixation of the posterior malleolus fracture.

We are acknowledged that our study has some limitations. These limitations are the small sample size, the retrospective and single-centre nature of the study, the fact that the decision of posterior malleolus fixation was left to the surgeon, and the relatively short follow-up period to evaluate long-term results. Although trimalleol fractures were diagnosed in all patients in our study, the types, fixation and quality of reduction of medial and lateral malleolus fractures were not evaluated. Furthermore, the development of posttraumatic arthritis may be associated not only with posterior malleolus fractures but also with other malleolus fractures and this uncertainty should be taken into consideration. Multicentre prospective randomized controlled studies with greater sample size and duration of follow-up should be performed to provide further evidence for these findings.

5. Conclusion

In conclusion, our study indicates that while fixation of Haraguchi type 1 posterior malleolus fractures less than 25% of the ankle joint improves radiological outcomes, clinical results remain comparable to conservative treatment. No differences between groups in terms of the development of arthrosis suggest that preservation of joint congruity may be more important than fixation in preventing posttraumatic ankle osteoarthritis. Further research with larger samples is necessary to validate these findings.

Conflict of Interest:
The authors declare that they have no conflict of interest.

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Ethics Approval: All methods were carried out in accordance with relevant guidelines and regulations. This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained by the Izmir Katip Celebi University Atatürk Training and Research Hospital Health Research Institutional Review Board (No:0066).

Consent to Participate: Consent to participate was obtained from all patients for being included in this study.

Consent for Publication: Not applicable.

Informed Consent:
Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data and photographs.

Competing Interest:
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All the authors contributed to the study's conception and design. Material preparation, data collection, and quality assessment were performed by M.M. and T.B. Statistical analysis and literature review were performed by M.M., O.D.A and I.A. The first draft of the manuscript was written by M.M. and C.O., and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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No artificial intelligence was used for the writing of the submitted work.

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Evaluation of Daytime Sleepiness Levels According to Types of Epilepsy

Metin Balduz[1], Halit Fidancı[1]

1 Department of Neurology, University of Health Sciences Adana City Training and Research Hospital, Adana, Türkiye

Abstract

Aim: This study aimed to investigate the relationship between electroencephalogram (EEG) findings, clinical characteristics, and subjective sleep measures in adult patients with epilepsy.

Methods: In this study, 105 patients previously diagnosed with epilepsy were included. EEG recordings were analyzed for interictal epileptiform discharges. Participants were divided into two groups: generalized and focal epilepsies, patients with focal epilepsy were also divided into subgroups. The Jenkins Sleep Scale (JSS) and Epworth Sleepiness Scale (ESS) were used to assess sleep quality and daytime sleepiness, respectively. Statistical data were obtained by making pairwise comparisons between groups.

Results: This study revealed that there was a significant association between EEG findings and gender, with frontal lobe epilepsy (FLE) more prevalent in females and temporal lobe epilepsy (TLE) more common in males. According to treatment modalities, monotherapy was predominant in patients with FLE and TLE, but statistically there was no difference across the groups. EEG abnormalities varied, with temporal and generalized abnormalities most prevalent. Significant differences were found in ESS and JSS scores across epilepsy groups, with higher scores observed in FLE. A positive correlation was found between ESS and JSS scores.

Conclusion: The impact of epilepsy on various aspects of a person's life, including sleep, is significant. This study underscores the importance of conducting comprehensive sleep assessments in clinical practice for individuals with epilepsy.

Keywords: *Epilepsy; sleep; Epworth; Jenkins*

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, and it is associated with a wide range of comorbid conditions, including sleep disturbances. Patients with epilepsy often experience both nocturnal and daytime sleep-related issues, which can exacerbate their condition and reduce their overall quality of life. Previous studies have shown that sleep disturbances, such as excessive daytime sleepiness, are common in epilepsy patients, but the mechanisms underlying these disruptions are not fully understood. While focal and generalized epilepsy types have distinct clinical presentations, their impact on sleep may differ [1].

Epilepsy and sleep disorders often coexist with many neurological or psychiatric conditions, which can affect epileptic seizure frequency and sleep quality[2]. Disruptions in sleep patterns can exacerbate the condition in patients with epilepsy[3]. Concurrently, the rise in seizure frequency may disturb patients' sleep structure and contribute to sleep disorders[3].

Some types of epilepsy are more likely to occur during specific stages of sleep, such as nocturnal seizures that occur during non-REM (rapid eye movement) sleep or during transitions between sleep stages[3]. In Frontal lobe epilepsy (FLE) seizures can disrupt the normal progression of sleep stages, leading to fragmented sleep and alterations in sleep architecture. These disruptions may result in excessive daytime sleepiness, fatigue, and impaired daytime functioning[4, 5]. Conversely, some studies suggest that sleep architecture is more disturbed in adults with temporal lobe epilepsy (TLE) compared with other types of epilepsy[1].

This study employed a prospective, observational design in adult patients with epilepsy to investigate the relationship between electroencephalogram (EEG), clinical findings, JSS and ESS scores.

2. Materials and Methods

This study was carried out in the Neurophysiology laboratory of Adana City T&R Hospital between 1 December 2022 and 1 March 2023. Patients aged 18 and over were included in the study and epilepsy was diagnosed according to the ILAE 2017 guideline[6].

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The EEG examinations were evaluated by a neurologist and a neurophysiologist separately for a specific epileptiform abnormality, the interictal spike or sharp wave. For a transient to be considered a specific interictal epileptiform discharge, at least 5 criteria had to be fulfilled according to the International Federation for Clinical Neurophysiology (IFCN) definition of interictal epileptiform discharge: (1) Di- or tri-phasic wave with pointed peak; (2) different wave duration than the ongoing background activity; (3) asymmetry of the waveform; (4) followed by a slow after-wave; (5) the background activity is disrupted by the presence of the IEDs; and (6) voltage map with distribution of the negative and positive potentials suggesting a source in the brain corresponding to a radial, oblique, or tangential orientation of the source[7, 8].

Electroencephalography recordings were performed in a dimly lit room at an outpatient neurophysiology laboratory using the standard 10-20 measuring system and gold disc electrodes affixed with Ten20 conductive paste (Weaver and Company, Norwalk, CA). The participants were relaxed and in a lying position. They were asked to abstain from alcohol for 24 h and coffee for 2 h before recording. To minimize the impact of external factors, eyes closed EEG was recorded. The 19-channel EEG was recorded for 20 min at least. The Cadwell Sierra Summit EEG (Cadwell Laboratories, Kennewick, Washington, USA).) device was used for recordings. The signals from 19 channels Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2 were recorded using the electrode Cz as reference. The raw EEG signal was recorded at the sampling frequency of 256 Hz, a high-pass filter of 0.53 Hz, a low-pass filter of 70 Hz and impedances of less than 5 kΩ. The primary montage used was the "longitudinal anatomic bipolar montage" with the option for rederivation to a different montage. Patients were reclined comfortably during the recordings, which lasted between 25 and 30 minutes. Reactivity was measured with eye opening and closing while patients were awake and alert. Photic stimulation was performed at rates of 1, 3, 6, 12, 15, 18, 20, and 30 Hz, for 10 seconds each, with 10 seconds in between. Hyperventilation was performed for three minutes unless medically contraindicated. The remaining study time was dedicated to quiet recording to facilitate drowsiness or sleep. EEG reports were analyzed using visual analysis and manual counting by a fellowship-trained neurophysiologist.

The Jenkins Sleep Scale (JSS) is used to assess various aspects of sleep quality and disturbances [9]. The scale was designed to evaluate the sleep onset, sleep maintenance, sleep duration and overall sleep quality. The respondents answer the questions using a six-point Likert-type scale. Total scores range from 0-20, and higher scores indicate a greater number of sleep problems[10].

The Epworth Sleepiness Scale (ESS) is a questionnaire that assess the likelihood of falling asleep in different situations commonly encountered in daily life. Individuals rate items in this questionnaire on a scale from 0 (never) to 3 (high probability), indicating the likelihood of them dozing off or falling asleep while engaged in various activities[11].

Both the Jenkins Sleep Scale and the Epworth Sleepiness Scale are valuable tools for assessing sleep quality and daytime sleepiness, respectively, and are frequently used in combination with objective measures of sleep to provide a comprehensive evaluation of sleep disorders and their impact on individuals' lives. Participants were provided with printed copies of the JSS and the ESS questionnaires along with instructions for completion. Participants completed the questionnaires in a quiet and comfortable environment, without time constraints. Research staff were available to answer any questions and clarify instructions if needed. Once participants completed the questionnaires, they returned them to the research staff for scoring and data entry.

The total score of ESS is calculated by summing the ratings across all items, with scores typically ranging from 0 to 24. Scores above 10 are considered indicative of excessive daytime sleepiness. The cutt-off value for the JSS-TR was determined to be 6.5 for differentiates between poor and good sleepers[12].

We excluded patients with diagnostically inconclusive and patients with nonepileptic paroxysmal events. Additionally, patients with diseases that may occasionally reveal IEDs like dialysis dementia, hypocalcemia, uremic encephalopathy, acute or chronic renal failure, nonketotic hyperglycemia, metabolic encephalopathies, eclampsia, thyrotoxicosis, and Hashimoto's encephalopathy were excluded.

For the expected specificity of 80%, with a significance level of % 10 and a power of 0.8, we needed at least 44 patients[13].

This study has received ethical approval from the Adana City T&R Hospital ethics committee (date: 17.11.2022, no: 116/2250), and all participants agreed to be included in this study by filling out an informed consent form.

2.1.Statistical analyses

Descriptive statistics were used to summarize demographic characteristics and sleep study variables. EEG findings were classified based on established criteria for sleep staging and identification of epileptiform abnormalities. Jenkins Sleep Scale scores were analyzed to assess subjective sleep quality, while Epworth Sleepiness Scale scores were used to quantify daytime sleepiness. Correlation analyses, such as Pearson correlation coefficients or Spearman rank correlations, were conducted to explore associations between EEG findings and subjective sleep measures.

The Independent-Samples Kruskal-Wallis test was conducted to assess whether there were statistically significant differences in epilepsy groups (frontal, generalized, and temporal) among the samples. Pairwise comparisons were then conducted to further examine the differences between specific pairs of groups. The adjusted significance level was set at .050, and the Bonferroni correction was applied to account for multiple comparisons.

3. Results

A total of 105 participants were included in the study. The mean age was 31.02±12.15 in all individuals. The gender distribution was nearly equal, with 52 (49.5%) females and 53 (50.5%) males. The mean duration of epilepsy was 11.18±9.25 years. Types of epilepsy varied among participants, with the most common being focal [temporal 38 patients (36.2%) and frontal 17 patients (16.2%), totally 55 (52.4%)], followed by generalized [50 patients (47.2%)], Most participants (65.7%) had normal MRI findings.

The distribution of patients across frontal, temporal, and generalized EEG findings significantly differed by gender ($p = 0.018$). Frontal lobe epilepsy was more commonly observed in females (62.0%), while temporal lobe epilepsy was more prevalent in males (76.5%).

Regarding treatment modalities, while no statistically significant difference was observed ($p = 0.136$), monotherapy was the predominant treatment approach for patients with frontal (68.0%) and temporal (52.9%) lobe epilepsies, whereas polytherapy was more common in generalized epilepsy (52.6%).

The incidence of head injury was low across all groups, with the temporal lobe epilepsy group showing the highest percentage (35.3%). Abnormal MRI findings were most frequent in patients with temporal lobe epilepsy (70.6%).

Comparative data between the epilepsy groups is presented in **table 1**.

Table 1

Comparative data between the groups

	Generalized epilepsy Mean±SD (Median)IQR	Frontal lobe epilepsy Mean±SD (Median)IQR	Temporal lobe epilepsy Mean±SD (Median)IQR	p
Epilepsy duration (year)	10.8±8.8 (8.5) 13.2	12.5±11.8(8)16.5	10.9±8.6(9)14.25	0.971
JSS score	6.4±4.1(6)7.2	9.2±3.6(11)2.5	5.8±4.5(4.5)8	0.016
ESS score	6.1±3.8(6)6	11±4.8(13)5	5.8±4.3(5)8.2	<0.001
Seizure frequency	5.5±4.9(4)3.7	7.1±8.3(4)7.5	6.2±4.7(5.5)5	0.713
Age	27.1±10.1(24)14.2	31.0±12.7(27)14.5	36.0±12.7(34)17.7	0.002

JSS: jenkins sleep scale, ESS: Epworth sleepiness scale, SD:Standard deviation, IQR: inter quantile range

A significant difference in age across epilepsy groups was found (p = 0.002). Participants with temporal lobe epilepsy were significantly older compared to generalized epilepsy (p = 0.001).

The mean of EDSS in focal and generalized epilepsy patients were 7.47±5.0 and 6.18 ± 3.82 (p=0.201) and JSS were 6.90 ± 4.49 and 6.42± 4.10 (p=0.501) respectively. The Independent-Samples Kruskal-Wallis test revealed a significant difference in ESS scores across epilepsy subgroups (p < 0.001). Post-hoc pairwise comparisons indicated that participants with frontal lobe epilepsy had significantly higher ESS scores compared to those with temporal lobe epilepsy (p = 0.001) and generalized epilepsy (p = 0.001) (**figure 1**).

While analysing the JSS scores, patients with frontal lobe epilepsy had statistically higher scores than patients with temporal lobe epilepsy and generalized epilepsy (p=0.015, p=0.044, respectively) (**figure 2**).

Spearman correlation analysis showed a significant positive correlation between Epworth Sleepiness Scale scores and Jenkins scores (p < 0.001). The mean JSS score was 6.67±4.3 and ESS score was 6.85±4.5.

No significant differences were found in epilepsy duration, seizure frequency, or gender distribution among the groups (p > 0.05).

Figure 2

Jenkins scale scores across the types of epilepsy

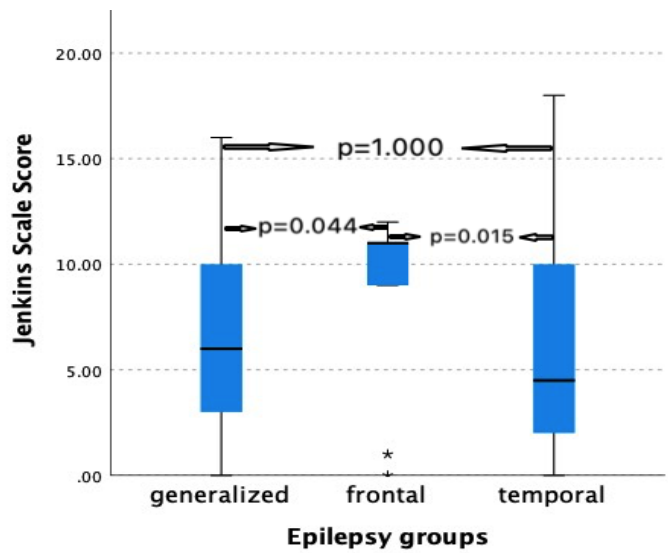
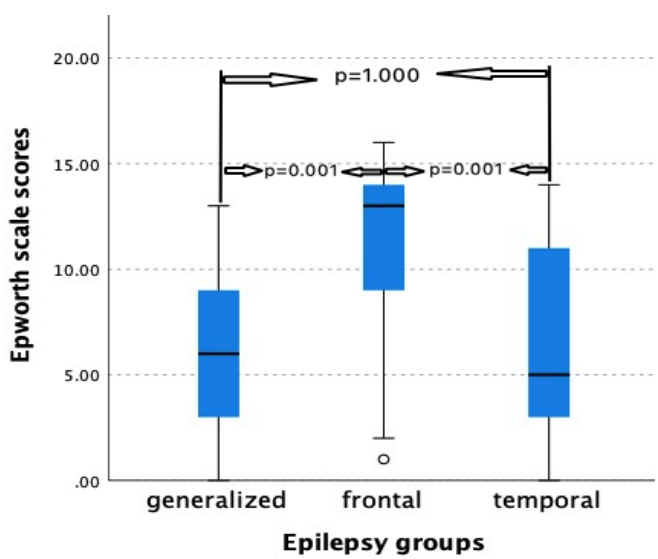


Figure 1

Epworth scale scores across the types of epilepsy



4. Discussion

The findings of this study underscore the importance of sleep-related symptoms in the clinical management of epilepsy. Our findings corroborate existing literature regarding the diverse clinical characteristics of epilepsy.

The wide age range and duration of epilepsy in our study population are consistent with previous reports highlighting the chronic and heterogeneous nature of the condition[14, 15].

Consistent with prior studies[14, 15], our findings indicated that temporal and generalized abnormalities were prevalent EEG patterns among patients with epilepsy. Temporal lobe epilepsy, characterized by seizures originating in the temporal lobes, often exhibits corresponding EEG abnormalities such as focal spikes or sharp waves[14]. Similarly, generalized epilepsy syndromes typically present with diffuse EEG abnormalities involving both hemispheres[15]. Our study's lower prevalence of frontal abnormalities aligns with some previous research[16] although discrepancies across studies suggest potential variability in EEG patterns among different epilepsy populations.

Tailored interventions that consider the multifaceted nature of the condition, including both seizure control and comorbidities such as sleep disturbances and stress, are essential for optimizing patient

outcomes[17]. Integrating EEG monitoring with comprehensive assessments of sleep and psychosocial functioning can inform individualized treatment plans and improve overall quality of life for patients with epilepsy[18].

Regarding sleep disturbances, our findings suggested that patients with epilepsy experienced varying degrees of daytime sleepiness, as evidenced by ESS scores ranging from 0 to 16. While the mean score of 6.86 fell within the mild to moderate range of sleepiness, it was crucial to recognize that excessive daytime sleepiness could have significant implications for quality of life and cognitive function in individuals with epilepsy. Byars et al. found a higher prevalence of sleep disorders in children with epilepsy[19]. Lack of sufficient sleep or poor sleep quality can increase the likelihood of experiencing seizures in individuals with epilepsy. Conversely, seizures themselves can disrupt sleep, leading to a cycle of sleep deprivation and increased seizure susceptibility[1].

In a previous study, it was shown that in patients with chronic epilepsy insomnia symptoms and short sleep duration were more common than recently diagnosed[20]. In another study, sleep architecture can be abnormal in children with primary generalized epilepsy[21]. In another previous study, Herman refers to a comprehensive review of sleep disorders in epilepsy, which would cover topics like excessive daytime sleepiness and the different impacts of epilepsy types on sleep. Some researchers believe that there may be common underlying mechanisms contributing to both epilepsy and certain sleep disorders, such as alterations in neurotransmitter systems or abnormalities in brain structures involved in regulating sleep-wake cycles. Moreover, our study revealed a wide range of Jenkins scores, indicative of varying levels of perceived stress among participants. Stress is known to be a common comorbidity in epilepsy, with potential implications for seizure control and overall well-being. Our findings underscore the importance of assessing and addressing stress in the management of epilepsy.

Seizures originating from the frontal lobe can have a significant impact on sleep architecture and contribute to sleep disturbances in affected individuals5, 22. Additionally, there is evidence to suggest that sleep disorders may also influence the occurrence and severity of seizures in individuals with FLE[2, 3]. Crespel and colleagues found that sleep architecture was more disturbed in 15 patients with mesial TLE compared with 15 with FLE. The patients with TLE had reduced sleep efficiency, increased Wakefulness after sleep onset (WASO), and more arousals[23]. Specifically, patients with frontal abnormalities tended to report higher scores on the ESS and JSS compared to those with temporal or generalized abnormalities in this study. The frontal lobe, particularly the prefrontal cortex, is involved in regulating the sleep-wake cycle. It receives input from other brain regions involved in circadian rhythm regulation and plays a role in promoting wakefulness during the day and initiating sleep at night. Frontal lobe seizures often occur during sleep, particularly during non-REM (rapid eye movement) sleep stages. These nocturnal seizures can disrupt sleep continuity and lead to awakenings during the night, further exacerbating sleep disturbances[3]. Seizures originating in the frontal lobes can disrupt the normal progression of sleep stages, leading to fragmented sleep and alterations in sleep architecture. These disruptions may result in excessive daytime sleepiness, fatigue, and impaired daytime functioning[24]. Sleep disorders such as insomnia, obstructive sleep apnea, or restless legs syndrome may lead to sleep deprivation or fragmentation, increasing the likelihood of seizures in individuals with FLE. Sleep deprivation can lower the seizure threshold and trigger epileptic activity in the frontal lobes.

While previous research has identified associations between specific EEG patterns and sleep disorders such as sleep apnea[25], our findings suggest broader relationships with daytime sleepiness and perceived stress. These associations underscore the complex interactions between epilepsy, sleep regulation, and stress response systems[24], highlighting the importance of comprehensive care approaches that address both clinical and psychosocial aspects of the condition.

Limitations of this study included its observational design, which precluded establishment of causality, and the relatively small sample size. Additionally, the study population consisted of patients presenting with sleep-related complaints, which may limit generalizability to other populations.

5. Conclusion

In conclusion, this study highlights the critical role of sleep disturbances, particularly excessive daytime sleepiness, in the clinical management of epilepsy These results suggest that patients with epilepsy, particularly frontal lobe epilepsy, may be affected by sleepiness. By demonstrating significant differences in ESS and JSS scores across epilepsy subtypes, our findings align with and extend existing literature, suggesting that sleep disturbances may serve as both a consequence and a contributing factor to seizure activity. This underscores the need for tailored interventions addressing sleep comorbidities to improve patient outcomes

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval

All methods were carried out in accordance with relevant guidelines and regulations. This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained by the Adana City T&R Hospital ethics committee (date: 17.11.2022, no: 116/2250).

Consent to Participate

Consent to participate was obtained from all patients for being included in this study.

Consent for Publication

Not applicable.

Informed Consent

Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data and photographs.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Author Contributions

All the authors contributed to the study's conception and design. Material preparation, data collection, and quality assessment were performed by MB. & HF. Statistical analysis and literature review

were performed by MB. The first draft of the manuscript was written by MB. & HF. and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Artificial Intelligence statement

No artificial intelligence was used for the writing of the submitted work.

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Effect of Respiratory Functions, Quality of Life, Anxiety and Depression on the Number of Exacerbations in Patients with Chronic Obstructive Pulmonary Disease

Leyla Çevirme[1], Gündeniz Altıay[2]

1 Department of Allergy and Immunology, Adana City Training and Research Hospital, Adana, Türkiye
2 Department of Chest Disease, Trakya University Hospital, Edirne, Türkiye

Abstract

Aim: Diagnosis and treatment of comorbidities in chronic obstructive pulmonary disease (COPD) facilitates the control of the disease, and evaluation and improvement of quality of life is an important part of the follow-up of the disease. Therefore, this study aimed to investigate the effects of pulmonary function, quality of life, anxiety and depression on exacerbations in COPD

Methods: Between May 2007 and May 2008, 70 patients with COPD admitted to the pulmonary medicine outpatient clinic were included in the study and followed up for one year in terms of exacerbations. Quality of life questionnaires and anxiety and depression assessment scale were applied at the first interview.

Results: The mean age of the patients was 64.24±10.62 years. The male patients was 88.6% and there was a significant correlation between gender and number of exacerbations (p=0.045). No significant correlation was found between respiratory functions and depression and the number of exacerbations (p=0.368, p=0.134, respectively). There was a moderate positive correlation between exacerbations and anxiety (p<0.001, r=0.468). Patients with lower quality of life questionnaire scores had significantly more frequent exacerbations. The physical (p=0.004) and mental (vitality and mental role limitation) subscales of the Short form-36, the independence (p=0.011) and physical (p=0.031) subscales of the World Health Organization Quality of Life-103, and the symptom (p=0.005), effect (p=0.001) and total (p=0.004) subscales of the St. George's respiratory questionnaire were significantly associated with the number of exacerbations.

Conclusion: Similar to the studies in the literature, this study revealed that male gender, anxiety and poor quality of life are associated with number of exacerbations in COPD, a systemic, irreversible disease characterized by exacerbations. Based on this, better exacerbation control can be achieved by improving the quality of life and treating the accompanying psychological factors with the utilization of quality of life questionnaires and scales assessing psychological status in the follow-up of patients with COPD.

***Keywords**: Anxiety; Chronic obstructive pulmonary disease; depression; exacerbation; Quality of life*

1. Introduction

Chronic obstructive pulmonary disease (COPD) is associated with intermittent exacerbations characterized by acute deterioration in symptoms of chronic breathlessness, cough and sputum production. Hospitalizations for acute exacerbations constitute the most important part of patient care. The presence of depressive symptoms in COPD patients is associated with an increase in severe exacerbations, decreased physical activity, increased dyspnea and impaired quality of life[1-2].

As in all chronic diseases, COPD, in addition to the organ dysfunction it causes, increases concerns about the future due to factors such as continuous medication use and hospital dependency, and leads to hopelessness and anxiety[3]. Anxiety and depression are the most common mental disorders in chronic respiratory system diseases. Numerous studies indicate an increased incidence of depression and anxiety in COPD patients. Although comorbid psychological symptomatology has been reported in 22-48% of people with COPD, most of the literature focuses on identifying risk factors for anxiety or depression separately[3]. Despite such a high prevalence, these two conditions often go unrecognized and untreated.

In chronic diseases, quality of life is further impaired by comorbid depression. The physical symptoms and social isolation caused by chronic disease lead to depressive effect, while depression decreases the ability to fight the disease and makes it difficult to tolerate the disease. Risk factors for COPD exacerbations include poor

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quality of life, decreased physical activity, and frequent exacerbations, which may be directly or indirectly related to the effects of patients' mental disorders associated with COPD[1-4]. Rehospitalization for exacerbation is common and occurs in 60% of patients within 1 year following the last exacerbation[4]. In one study, depression and anxiety were associated with a higher risk of recurrence in COPD patients admitted for emergency treatment[5]. Cognitive and behavioral therapy applied to COPD patients has been shown to increase exercise capacity[6]. Quality of life deterioration in COPD is reflected by decreased energy, mobility and sleep, emotional disturbance, anxiety, depression, dissatisfaction with life and somatic preoccupation. Underlying symptoms of anxiety and/or depression are often underreported, underdiagnosed and undertreated. It may predict severe respiratory exacerbations and severity of COPD and asthma leading to impaired quality of life and increased healthcare utilization compared to patients without these symptoms[7]. Our aim was to investigate the impact of respiratory function, quality of life, anxiety and depression on exacerbations in COPD patients.

2. Materials and Methods

Between May 2007 and May 2008, 70 consecutive outpatients with COPD admitted to Trakya University Medical Faculty Chest Diseases Outpatient Clinic and staged according to the Global Initiative for Chronic Obstructive Lung Disease guidelines (postbronchodilator FEV1/FVC ratio <0.70 and GOLD 1 FEV1≥80%, GOLD 2 FEV1 50-79%, GOLD 3 30-49%, GOLD 4: <30%) were included in the study. Patients with pregnancy, active autoimmune disease, or active malignancy were excluded from the study. The study was planned prospectively. According to the number of exacerbations, patients with more than 2 exacerbations were classified as group E, and those with 0 or 1 exacerbation were classified as group A/B (GOLD)[9]. The Effect of Respiratory Functions, Quality of Life, Anxiety and Depression on The Number of Exacerbations in Chronic Obstructive Pulmonary Disease Patients The quality of life questionnaires, St. George's Respiratory Questionnaire (SGRQ), Short-Form36 (SF-36), World Health Organizations Quality Of Life -103 (WHOQOL-103) and Hamilton anxiety (HADS-A) and depression (HADS-D) rating scale were administered to the patients at the first interview. Patients were followed up for one year in terms of the number of exacerbations. At the end of one year, the total number of exacerbations was recorded. As exacerbation criteria, the criteria defined by Anthonisen et al. were used[8]. These were an increase in worsening of dyspnea, sputum volume and purulence. Approval for the study was obtained from the local ethics committee (03.04.2008 date and 07/09 number of). Written informed consent was also obtained from each patient. The principles of the Helsinki Declaration were adhered to throughout the study.

2.1. Statistical analysis

The conformity of the data to normal distribution was analyzed by one sample Kolmogorov Smirnov test. Independent samples t test was used for variables showing normal distribution, Mann Whitney U test and Spearman correlation analysis were used for variables not showing normal distribution in the investigation of differences between the number of exacerbations (0-1, ≥2) and stage (1-2,3-4) groups. Chi-square test was used to investigate the difference of categorical variables between groups. P<0.05 was accepted as the limit of statistical significance. Statistica 7.0 (Serial Number: 31N6YUCV38, Edirne/ Türkiye) package program was used for statistical analysis.

3. Results

The mean age of the patients included in the study was 64.24±10.62 years and 88.6% were male. Of the patients, 6% were non-smokers, 73.1% were former smokers and 20.9% were smokers. The distribution according to stages was as follows; 17.1% patients were in GOLD stage 1, 45.7% patients were in GOLD stage 2, 20% patients were in GOLD stage 3 and 17.1% patients were in GOLD stage 4. 62.9% of the patients had 0-1 exacerbations and 37.1% had ≥2 exacerbations. The mean number of exacerbations was 1.24±1.39. The mean anxiety score was 15.30±6.36 (HADS-A). Depression was not detected in 90% of the patients, mild depression was detected in 7.1% and major depression was detected in 2.9%. The mean depression score was 2.84±3.70 (HADS-D). **Table 1** shows the overall characteristics of the patients included in the study.

Table 1

General characteristics of the patients in the study (n:70)

General characteristics of the patients	n(%)
Age	64.24±10.6
Gender	
Man	62 (88.6)
Women	8 (11.4)
Smoke status	
Nonsmoker	4 (6)
Ex smoker	52 (73.1)
Smoker	14 (20.9)
Stage	
1	12 (17.1)
2	32 (45.7)
3	14 (20)
4	12 (17.1)
Number of Exacerbation	1.24 ±1.39
Anxiety score	15.30±6.36

Table 2

Relationship between the number of Exacerbation and age, gender, marital and educational status

		Number of exacerbation 0-1 (n=44) n (%)	≥2 (n=26) n (%)	p
Age		64.50 ±11	63.69±10	0.742
Gender	Woman	2 (4.5)	6 (23.1)	0.045
	Man	42 (95.5)	20 (76.9)	
Marital status	Single	1 (2.3)	0 (0)	0.599
	Married	40 (90.9)	23 (88.5)	
	Divorced	3 (6.8)	3 (11.5)	
Education Status	Illiterate	1 (2.3)	1 (3.8)	0.989
	Primary School	31 (70.5)	18 (69.2)	
	Middle school	4 (9.1)	2 (7.7)	
	High school	4(9.1)	3 (11.5)	
	College	4 (9.1)	2 (7.7)	

Table 3

Distribution of stages according to the number of exacerbation

	Number of exacerbation n (%)		p
	0-1	≥2	
1	7 (15.9)	5 (19.2)	0.923
2	21 (47.7)	11 (42.3)	
3	8 (18.2)	6 (23.1)	
4	8 (18.2)	4 (15.4)	

Eight (11.4%) of the patients were female. Of the female patients, 25% had 0-1 exacerbation and 75% had ≥2 exacerbations. Among male patients, 67.7% had 0-1 exacerbations and 32.3% had ≥2 exacerbations. There was a significant difference between patients with 0-1 and ≥2 exacerbations in terms of gender distribution (p=0.045). **Table 2** shows the demographic characteristics of the patients included in the study according to the number of exacerbations.

The distribution of the patients according to stages was as follows; 17% were in stage 1, 45.7% in stage 2, 20% in stage 3 and 17.1% in stage 4. There was no significant difference between the stages according to the number of exacerbations (p=0.923). There was also no significant difference between the number of 0-1 exacerbations and ≥2 exacerbations in patients grouped as stage 1-2 and stage 3-4 (p=0.861). **Table 3** shows the distribution of patients staged according to GOLD according to the number of exacerbations.

Quality of life of the patients included in the study was measured with general and disease-specific tests. Between patients with 0-1 and ≥2 exacerbations, the physical of the SF-36 was measured as physical impact (p=0.009), physical role limitation(p=0.010), general health (p=0.002) and the mental health was measured as vitality (p=0.020), mental role limitation (p=0.018). 018), physical health (p=0.031) and independence (p=0.011) of WHOQOL 103, symptom (p=0.005), impact (p=0.001) and total score (p=0.004) of SGRQ (**Table 4**).

Figure 1

Correlation between anxiety score and number of exacerbation

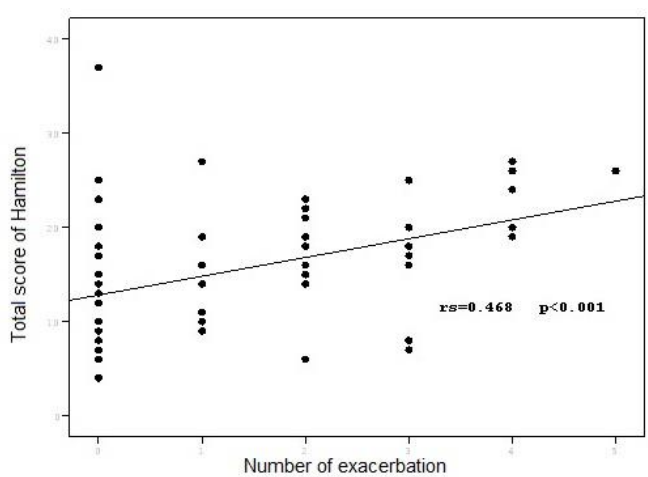

Table 4

Distribution of the number of exacerbation and quality of life questionnaire scores

		Number of exacerbation		p	
		0-1	≥2		
SF-36(PHA)	Physical function	63.64±32.82	40.58±33.20	0.009	0.004
	Physical role limitation	60.80±46.81	29.81±43.02	0.010	
	Pain	77.75±17.59	72.15±18.65	0.154	
	General health	61.02±19.27	45.19±22.24	0.002	
SF-36(MHA)	Social function	67.61±24.90	61.54±23.69	0.384	0.093
	Mental role limitation	68.94 ±44.54	42.31±47.66	0.018	
	Sanity	66.27±22.03	58.15±21.50	0.112	
	Energy	62.73±20.35	50.19±21.23	0.020	
WHOQOL-103	Physical health	69.50±16.40	59.69±18.25	0.031	
	Psychological health	72.30±13.51	69.37±16.74	0.515	
	Level of independence	71.16±17.85	57.63±21.19	0.011	
	Social area	63.78±13.76	60.50±15.54	0.480	
	Environment	71.92±12.744	65.44±16.73	0.127	
	Personal beliefs	74±19.80	71.63±21.88	0.676	
	Social pressure	83.77±19.88	76.03±24.58	0.165	
SGRQ	Symptom	46.84±21.55	61.80±17.33	0.005	
	Activity	51.24±33.94	65.42±27.89	0.092	
	İmpact	25.28±22.23	45.36±22.53	0.001	
	Total	36.83±22.85	54.21±20.08	0.004	

SF-36: Short Form-36, PHA: Physical Health Area, MHA: Mental Health Area WHOQOL-103: World Health Organization Quality Of Life-103, SGRQ: St George's Respiratory Questionnaire.

Depression was absent in 90% of the patients. There was no statistically significant relationship between those with 0-1 exacerbations and those with ≥2 exacerbations in terms of depression (p=0.134) (**Table 5**).

Table 6 shows the Hamilton anxiety score according to the number of exacerbations. Hamilton anxiety total score (HADS-T) was 13.48±6.18 in patients with 0-1 exacerbations and 18.38±5.52 in patients with ≥2 exacerbations. There was a statistically significant difference between patients with 0-1 exacerbations and patients with

≥2 exacerbations in the anxiety score (p<0.001) and total score (p<0.001).

While a moderate positive correlation was found between the number of exacerbations and anxiety score (r=0.468; p<0.001), no significant correlation was found between depression scores (r=0.054; p=0.655) (**Figure 1**).

The mean FEV1 was 1.62 L in patients with 0-1 exacerbations and 1.48 L in patients with ≥2 exacerbations. No statistically significant relationship was found between the number of exacerbations and pulmonary function (p=0.368).

Table 5

Distribution of depression according to the number of exacerbation

	Number of exacerbation n (%)		p
	0-1	≥2	
None	40 (90.9)	23 (88.5)	
Mild	4 (9.1)	1 (3.8)	0.134
Major	0 (0)	2 (7.7)	

Table 6

Distribution of anxiety scores according to the number of exacerbation

	Number of exacerbation		p
	0-1	≥2	
Psychic	3.91±2.47	5.12±2.79	0.086
Somatic	9.57±4.41	13.15±3.80	0.000
Total	13.48±6.189	18.38±5.52	0.000

4. Discussion

In our study of 70 patients with COPD, we found a significant relationship between the number of exacerbations and low quality of life, male gender and anxiety. Patients with low quality of life scores and functional performance were found to have high number of exacerbations. Poor quality of life was found in the physical and mental subgroups of SF-36, WHOQOL-103 subgroups, symptom and impact subgroups of SGRQ and total score.

The prevalence of depression in COPD patients was 10%. There was no statistically significant relationship between the number of exacerbations and the presence of depression.

There was a moderate positive correlation between anxiety scores and number of exacerbations. It was observed that the disease was prevalent among males and increased with age. The gender difference is explained by the fact that males smoke more and more exposed to toxic substances due to their occupation. It is thought that this difference will disappear in the near future with the gradual increase in smoking habit in females[9]. In our study, in accordance with the literature, the majority of our COPD patients were male and older age.

In a study reported that SF-36 is a valid questionnaire to assess quality of life in COPD patients and its physical components are an indicator of exacerbation and mortality. In our study, general and disease-specific quality of life questionnaires were used[10]. Quality of life scores of patients with 0-1 exacerbation were compared with those with more than two exacerbations. A statistically significant difference was found in the physical health of SF-36 in the physical impact, physical role limitation, and general health groups; in the vitality and mental role limitation groups in the mental health domain. Additionally, a statistically significant difference was found in the physical health and independence level domains of WHOQOL 103; and in the symptom, impact and total scores of SGRQ (p<0.05). (**Table 5**). In a 416-patient study on hospital readmission due to exacerbation in COPD patients, some of the risk factors for exacerbation were decreased respiratory function, age, poor quality of life, and decreased physical activity. In the same study, patients readmitted to hospital (due to exacerbation) were found to have high SGRQ scores and low quality of life. This study showed that health status is an important risk factor for readmission[11].

A study found that impaired health status and high SGRQ scores were significant risk factors for hospital readmission in the next 12 months[12]. The EFRAM (Estudi del Factors de Risc d' Aguditzacio de la MPOC) study in Spain showed that high levels of physical activity reduced the risk of hospital readmission. Again, found that those who had the lowest score in the health status, sensory skills, scale of SF-36 used in the EFRAM study were at a higher risk of exacerbation[4]. Most of the mortality and morbidity in COPD can be attributed to exacerbations. Mortality due to exacerbations is gradually increasing[13]. It is thought that poor quality of life may reduce current life expectancy in COPD patients[14]. This shows the important relationship between exacerbations, mortality and quality of life. In a study of 321 stable COPD patients shown that SGRQ total score and SF-36 physical function score were associated with disease-specific and overall mortality in COPD patients[15]. In our study, as seen in many studies reported above, patients with low quality of life scores and functional performance were found to have frequent exacerbations.

Psychological conditions (anxiety and depression) accompanying morbidity in COPD are quite common and often associated with increased disability. These conditions also reduce quality of life and are often not investigated in the clinical management of COPD patients. Although different methods have been used in various studies, depression has been reported between 7-42% in COPD patients[16]. They found depressive disorder in 25% of COPD patients and anxiety in 44.4%. It is thought that shortness of breath, activity limitation and recurrent exacerbations in COPD lead to anxiety[17]. In a study conducted in 2005, significantly increased admission was found in the presence of anxiety in patients and no relationship was found between depression and admission due to an exacerbations. In the same study, a significant relationship was found between anxiety, depression and health status, and high SGRQ scores (low quality of life) were found in patients presenting with an exacerbations[18]. A study found that anxiety and depression were associated with a higher risk of relapse in asthma and COPD patients admitted for emergency treatment5. The EFRAM study found that patients with low health status were more likely to be admitted for an exacerbations[4]. One study found that patients with both chronic disease and depression had more functional impairment than patients with depression and chronic disease alone, and therefore these patients needed more primary care and emergency care[19-20]. In another study conducted to determine the level of anxiety in COPD patients, the anxiety score was found to be higher in the group with severe COPD, but the difference was not statistically significant[21].

In our study, we found a moderate positive correlation between anxiety scores and the number of exacerbations, which was similar to the literature. We found depression in 10% of our patients, but we did not find a statistically significant difference between the level of depression and the number of exacerbations. This may be due to

the wide range of demographic characteristics of the patients, the inclusion of patients from all stages in the study, and the patients' perception of depressive complaints as a part of their disease.

4.1. Limitations

The fact that the study was conducted between 2007 and 2008 is a limitation. This is because GOLD updates its guidelines annually. Additionally, the unequal distribution of male and female patients could influence the prevalence of anxiety and depression, which may pose another limitation for this study.

5. Conclusion

In our study, a significant correlation was found between the number of exacerbations and poor quality of life, male gender and anxiety. Based on this, we believe that the factors that constitute quality of life should be taken into consideration when determining the severity of the disease and evaluating treatment interventions and that the use of quality of life questionnaires in outpatient clinics would be appropriate. In addition to medical treatment, psychological and social assistance should be provided to improve quality of life and rehabilitation programs should be emphasized. Psychological problems accompanying the disease in COPD affect quality of life, patient compliance, treatment duration and costs, mortality and morbidity. Therefore, evaluating patients psychologically and treating appropriate patients will make it easier to control COPD. COPD should be considered as a chronic systemic disease and should be analyzed in all aspects. Future studies that utilize multi-center designs and incorporate various anxiety and depression scales, in accordance with the current GOLD criteria, could contribute significantly to the literature.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. Thesis Number: 230357, https://tez.yok.gov.tr/ https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=UPP_Zu9isEmWGFXFCBYasdZ3Av56qA9ZbZjHy1aVXBzTWP-Nr-wlfbrtN-aOcquf

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval

All methods were carried out in accordance with relevant guidelines and regulations. This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was obtained by the Trakya University ethics committee (03.04.2008 date and 07/09).

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

All the authors contributed to the study's conception and design. All the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Artificial Intelligence statement

No artificial intelligence was used for the writing of the submitted work.

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Treatment Options and Outcomes in Patients Presenting with Incarcerated Abdominal Wall Hernia at Our Clinic

Sedat Çarkıt[1], Mustafa Karaağaç[1]

1 Department of General Surgery, Erciyes University Faculty of Medicine, Kayseri, Türkiye

Abstract

Aim: The aim of this study is to evaluate the demographic characteristics, treatment methods, and outcomes of patients presenting with incarcerated hernia. This study investigates the rates of stoma and bowel resection application according to different types of hernia, as well as the effects of demographic variables such as age and gender on treatment options.

Methods: This study included 109 patients who were admitted to our clinic with incarcerated hernia between August 1, 2022, and August 1, 2024. Data such as age, gender, type of hernia, treatment method applied, and whether stoma or resection was performed were collected. Statistical analyses were conducted using SPSS 22.0 software, and the relationships between groups were evaluated using Pearson Chi-Square test, Likelihood Ratio test, and Linear-by-Linear Association test.

Results: Emergency surgical intervention was more frequently preferred in inguinal and femoral hernia cases, whereas follow-up treatment was more commonly applied in incisional hernias. The highest rate of stoma formation was observed in incisional hernias. A linear relationship was found between increasing age and the necessity for resection (p=0.022). A statistically significant relationship was observed between the type of hernia and the treatment method in certain cases (p=0.025).

Conclusions: Treatment approaches vary depending on hernia type and patient's age, with increased risk of complications in elderly patients. This study may contribute to the development of more appropriate treatment strategies.

Keywords: *Incarcerated hernia; emergency hernia repair; hernia-related complications; surgical outcomes in hernia; stoma and resection rates*

1. Introduction

Incarcerated hernia is a clinical condition that requires emergency surgical intervention and carries a high risk of complications. A hernia is defined as the protrusion of intra-abdominal organs through a defect or weak point in the abdominal wall. These organs can become trapped within the hernia sac, leading to incarceration, which can progress to strangulation and organ necrosis due to impaired circulation. This condition can lead to serious complications in the gastrointestinal system and potentially fatal outcomes[1]. Therefore, it is critical to determine a rapid and effective treatment strategy in patients diagnosed with incarcerated hernia.

Surgical intervention is generally the first choice in the treatment of incarcerated hernia, with emergency surgery being the most commonly applied method[2]. However, treatment options may vary depending on the type of hernia, the patient's overall condition, age, and comorbidities. In some cases, bowel resection or stoma formation may be required during surgery, and such procedures can directly affect the patient's short- and long-term prognosis. However, there is no consensus in the literature on which factors necessitate such additional surgical procedures in the treatment of incarcerated hernia[3]. Most existing studies are limited to small case series or retrospective analyses, and there is a need for more data on stoma and resection rates according to the type of hernia.

This study hypothesizes that there is a significant relationship between advanced age and the necessity for bowel resection in incarcerated hernia cases[3]. Additionally, it aims to investigate whether different hernia types influence treatment approaches and outcomes, particularly in terms of emergency surgery, stoma formation, and resection rates.

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The aim of this study is to evaluate the demographic characteristics, treatment processes, and outcomes of patients who presented to our clinic with incarcerated hernia. The study examines the rates of stoma and resection application by hernia type and the effects of demographic variables such as age and gender on treatment options and outcomes. These findings are expected to contribute to the development of more appropriate strategies in the treatment of incarcerated hernia and support clinical decision-making processes.

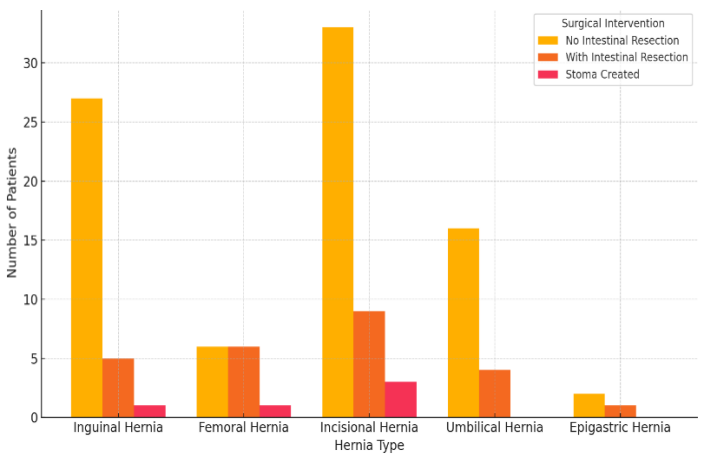
2. Materials and Methods

This study included 109 patients who presented to our General Surgery Clinic with a diagnosis of incarcerated hernia between August 1, 2022, and August 1, 2024. Data such as age, gender, type of hernia, treatment method applied (emergency surgery or follow-up), and whether a stoma or resection was performed were obtained from patient files. Patients who were not operated immediately underwent imaging studies, with IV contrast-enhanced abdominal CT being the preferred method to evaluate their condition. Clinically irreducible cases were taken directly to surgery. Additionally, patients managed with follow-up were later scheduled for elective surgery and underwent the procedure as planned. All patients included in the study were over 18 years of age, and their diagnosis and treatment processes were fully recorded. Rare types of hernia, such as obturator hernia, were excluded from the study. Patients with missing data were not included.

Patients with a history of previous hernia repair surgery were included in the study, provided that they presented with incarcerated hernia requiring urgent evaluation. Those with a history of prior intra-abdominal malignancy, advanced liver cirrhosis, severe coagulopathy, or end-stage renal disease were excluded.

Figure 1

Hernia Types Distribution Based on Surgical Interventions



The follow-up period for post-operative patients was at least 30 days, during which complications such as surgical site infection, bowel obstruction, and hernia recurrence were recorded.

All patients underwent a standardized diagnostic approach. Physical examination and detailed anamnesis were performed in all cases, followed by imaging. IV contrast-enhanced abdominal CT was the primary imaging modality used for incarcerated hernias, while bedside ultrasound was performed selectively in cases where immediate imaging was required.

The demographic and clinical data used in the study include variables such as age, gender, type of hernia (inguinal, femoral, incisional, umbilical, epigastric), stoma status (without stoma, with stoma), resection status (without resection, with resection), and treatment method applied (emergency surgery, follow-up). The data were obtained from the hospital information management system and patient files.

Statistical analysis was performed using SPSS 22.0 software. Descriptive statistics of demographic data were reported as mean, median, 25th and 75th percentiles for age, and frequency and percentage for categorical variables. Crosstab analyses were used to evaluate stoma and resection status by hernia type. Relationships between groups were evaluated using Pearson Chi-Square test, Likelihood Ratio test, and Linear-by-Linear Association test. Results with p-values below 0.05 were considered statistically significant. Fisher's Exact Test was used when the expected frequencies in the cells were less than 5.

3. Results

This study examined the demographic characteristics, stoma and resection application rates by hernia type, and treatment methods of patients presenting to our clinic with incarcerated hernia. A total of 109 patients were included in the study. The mean age was 68.64, and the median age was 70. The 25th percentile of ages was 61.50, the 50th percentile (median) was 70.00, and the 75th percentile was 77.00. The gender distribution showed that 40 of the 109 patients were male (36.7%), and 69 were female (63.3%). **Table 1** presents the demographic and clinical data of the patients.

Table 1

Demographic and Clinical Characteristics of Patients

Characteristics	%	n / Mean ± SD
Total Number of Patients		109
Female	63.3%	69
Male	36.7%	40
Average Age		68.64 years ± 11.20
Female Average Age		68.14 years ± 11.70
Male Average Age		69.5 years ± 10.36
Hernia Type		
Inguinal Hernia	29.4%	32
Femoral Hernia	11%	12
Incisional Hernia	38.5%	42
Umbilical Hernia	18.3%	20
Epigastric Hernia	2.8%	3

Among the patients diagnosed with inguinal hernia, 31 out of 32 were without a stoma, whereas only 1 patient presented with a stoma. Of the 12 patients presenting with femoral hernia, 11 did not have a stoma, while 1 patient had a stoma. Out of the 42 patients with incisional hernia, 39 were without stoma, and 3 had a stoma. In the umbilical hernia group, all 20 patients were without stoma. In the epigastric hernia group, all 3 patients were without stoma. Overall, 104 out of 109 patients were without stoma, and 5 had a stoma. These data indicate that stoma formation is rare in some types of hernia.

Figure 2

Age Group Distribution of Patients by Intestinal Resection Status with Chi-Square Analysis

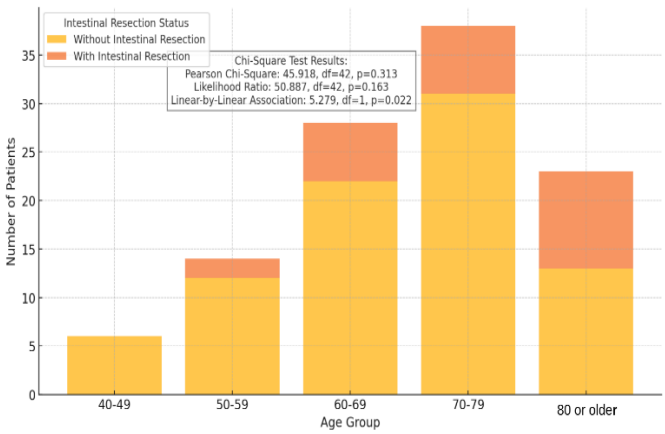


Table 2

Association Between Age and Resection Status in Incarcerated Abdominal Wall Hernia Patients.

Age	Non-Resection (n)	Resection (n)	Total (n)
40	1	0	1
42	2	0	2
43	1	0	1
44	1	0	1
46	1	0	1
49	1	0	1
50	1	0	1
52	0	1	1
53	3	0	3
54	1	0	1
55	1	0	1
56	1	0	1
57	2	0	2
58	2	1	3
59	3	0	3
60	1	0	1
61	3	0	3
62	3	1	4
63	1	0	1
64	3	1	4
65	2	0	2
66	3	0	3
67	1	3	4
68	2	1	3
69	3	1	4
70	3	1	4
71	5	1	6
72	4	1	5
73	4	1	5
75	3	0	3
76	2	2	4
77	4	0	4
78	3	0	3
79	3	0	3
80	1	4	5
81	2	4	6
82	1	0	1
83	1	0	1
85	2	0	2
86	1	1	2
87	0	1	1
89	1	0	1
91	1	0	1
Linear-by-Linear Association		P: 0.022	

When examining whether resection was performed by hernia type, 27 out of 32 patients with inguinal hernia were without resection, and 5 had resection. Among the 12 patients with femoral hernia, 6 were without resection, and 6 had resection. Out of 42 patients with incisional hernia, 33 were without resection, and 9 had resection. In the umbilical hernia group, 16 out of 20 patients were without resection, and 4 had resection. In the epigastric hernia group, 2 out of 3 patients were without resection, and 1 had resection. **Figure 1** graphically presents the patients who underwent resection and stoma.

In assessing the relationship between age and the performance of resection, most patients who underwent resection were 67 years or older. **Table 2** presents the age distribution of patients who required bowel resection compared to those who did not. **Figure 2** graphically presents the patients with and without bowel resection in hernias according to age. Chi-square tests were conducted to evaluate the statistical significance of this relationship. The Pearson Chi-Square test yielded a value of 45.918 (df = 42, p = 0.313), indicating no statistically significant association between age and the need for resection. Similarly, the Likelihood Ratio test resulted in a value of 50.887 (df = 42, p = 0.163). However, the Linear-by-Linear Association test showed a significant result (5.279, df = 1, p = 0.022), suggesting a potential trend where older patients may have a higher likelihood of requiring resection. Due to the low expected counts in some cells, these results should be interpreted with caution.

In the evaluation of treatment approaches based on hernia type, 25 out of 32 patients with inguinal hernia underwent emergency surgery, while 7 patients were managed with follow-up.

All 12 patients with femoral hernia underwent emergency surgery. Among the 42 patients with incisional hernia, 27 underwent emergency surgery, while 15 were followed up. In the umbilical hernia group, 15 out of 20 patients underwent emergency surgery, while 5 were followed up. In the epigastric hernia group, all 3 patients underwent emergency surgery. Overall, 82 out of 109 patients underwent emergency surgery, and 27 received follow-up treatment. **Table 3** shows the types of treatment by hernia type.

Table 3

Distribution of Hernia Types by Management Approach and Chi-Square Test Results

Hernia Type	Emergency Surgery (n, %)	Reduced Follow-Up (n, %)
Inguinal Hernia	25 (78.12%)	7 (21.87%)
Femoral Hernia	12 (100%)	0 (0%)
Incisional Hernia	27 (64.28%)	15 (35.72%)
Umbilical Hernia	15 (75%)	5 (25%)
Epigastric Hernia	3 (100%)	0 (0%)
Total Cases	82 (75.2%)	27 (24.8%)
Chi-Square Test Results	Value	p-value
Pearson Chi-Square	7.783	0.100
Likelihood Ratio	11.175	0.025
Linear-by-Linear Association	0.409	0.523
Number of Valid Cases	109	
Notes:	40% of cells have an expected count of less than 5. The minimum expected count is 0.74.	

When examining the statistical analysis results, the Pearson Chi-Square test value for the relationship between hernia type and stoma formation was 2.274 (p=0.686), indicating no significant relationship. However, a linear relationship was found between increasing age and the need for resection (p=0.022). For the relationship between hernia type and treatment method, the Likelihood Ratio test p-value was 0.025, indicating a statistically significant relationship in some cases.

4. Discussion

This study retrospectively evaluated the treatment methods and outcomes of patients diagnosed with incarcerated hernia. Our findings highlight the rates of various surgical interventions (e.g., bowel resection, stoma formation) according to hernia type and their association with demographic factors such as age. The analysis included patients with inguinal, femoral, incisional, umbilical, and epigastric hernias, and the results were compared with existing literature.

Emergency surgery was the predominant treatment approach for patients with inguinal hernia. In our cohort, 78.12% of patients underwent emergency surgery, while 21.87% were managed conservatively with reduction and follow-up. These findings align with the literature, which underscores surgical intervention as the primary treatment for inguinal hernias, with conservative management being less common [4,5]. Similarly, all cases of femoral hernia (100%) required emergency surgical intervention in our study. This observation is consistent with prior research highlighting the high risk of strangulation and necrosis in femoral hernias, necessitating urgent surgical treatment [6]. According to the European Hernia Society (EHS) guidelines, femoral hernias should be managed surgically as soon as possible due to their high risk of incarceration and strangulation [7]. Our findings support this recommendation and emphasize the need for prompt surgical intervention in these cases.

In patients with incisional hernias, 64.28% underwent emergency surgery, while 35.72% were followed up. This variability reflects the heterogeneous clinical course and complication potential of incisional hernias. The literature suggests that while follow-up may be appropriate in certain cases, emergency surgery is crucial for patients with high complication risks [5,8,9]. Our findings corroborate this variability, emphasizing the importance of individualized treatment strategies. The American College of Surgeons (ACS) suggests that incisional hernias with signs of incarceration or strangulation should be managed urgently to reduce the risk of complications[10]. Our study aligns with this recommendation, highlighting that a significant proportion of incisional hernias required emergency intervention.

The treatment distribution for umbilical and epigastric hernias also aligned with existing literature. Emergency surgical intervention was performed in 75% of patients with umbilical hernia, whereas 25% were managed conservatively. In contrast, all patients with epigastric hernia (100%) underwent emergency surgical intervention. These results suggest that although these hernia types are often less complex, their incarceration necessitates prompt surgical management. Clinical judgment remains critical in determining the appropriate treatment approach [11-113].

Our analysis of bowel resection and stoma formation rates by age revealed that bowel resection was more common in patients aged 67 years and older. While the association between age and bowel resection was not statistically significant (p:0.313), a linear trend was observed between increasing age and the need for resection (p:0.022). This outcome suggests that elderly patients presenting with incarcerated hernia are more likely to require intestinal resection, highlighting the importance of perioperative risk assessment and careful surgical planning in this population[14]. These results support the need for close monitoring and individualized management strategies in elderly patients to minimize morbidity and optimize postoperative outcomes[14]. This finding is consistent with previous studies reporting higher complication rates in elderly patients [14-16]. Considering these findings, early surgical intervention should be prioritized in elderly patients presenting with incarcerated hernia to potentially reduce the need for bowel resection and its associated morbidity[17].

Crucially, a statistically significant relationship was found between hernia type and treatment approach (p=0.025), suggesting that different hernia types may have a direct influence on the preferred management strategy. This result indicates that certain hernia types, particularly femoral and epigastric hernias, may require more aggressive surgical intervention due to their higher risk of strangulation and associated complications[7]. Understanding this relationship can aid in refining clinical decision-making and optimizing individualized treatment plans. Given the significant association between hernia type and surgical approach, future guidelines could incorporate stratification models to better define which patients benefit most from early surgical intervention[18].

Notably, stoma formation was more frequently required in patients with incisional hernias compared to other hernia types. This finding is in line with the literature, which identifies a higher complication risk in incisional hernias, often necessitating stoma formation. These results underscore the importance of heightened clinical vigilance in managing incisional hernias.

Differences in treatment methods were also observed across hernia types. A statistically significant relationship was found between hernia type and treatment approach in certain cases (p:0.025), suggesting that the clinical course and complication potential of specific hernia types influence treatment decisions. These findings advocate for more tailored treatment strategies for incarcerated hernias [19,20].

This study was conducted in a single center with a limited number of patients (n=109), which may restrict the generalizability of the findings to a broader population. Future multi-center studies with larger cohorts are needed to validate our results. As a retrospective study, our findings are subject to inherent limitations in data collection and potential selection bias. A prospective study design would provide more robust evidence regarding the causal relationship between hernia type, patient demographics, and surgical outcomes. The postoperative follow-up period in this study was at least 30 days, which may not be sufficient to assess long-term outcomes such as hernia recurrence and chronic complications. Future studies with longer follow-up durations are necessary. Although all patients underwent standardized diagnostic imaging (contrast-enhanced CT as the primary modality), variations in surgical techniques and perioperative management strategies may have influenced outcomes.

This study has several limitations. First, as a retrospective analysis, it is subject to inherent limitations in data collection. Additionally, being a single-center study with a relatively small patient population, the generalizability of the findings is limited. Future research incorporating data from multiple centers and larger cohorts is warranted to provide more robust evidence regarding the treatment options and outcomes for incarcerated hernias.

5. Conclusion

Our findings highlight the importance of considering hernia type, patient age, and general condition in determining treatment strategies for incarcerated hernias. The increased need for stoma in

incisional hernias and the higher risk of complications with advancing age emphasize the necessity of individualized approaches. Emergency surgical intervention remains crucial, particularly for femoral and epigastric hernias. These results contribute to improving clinical decision-making in the management of incarcerated hernias.

Statement of ethics

Ethical approval was obtained from the Erciyes University Faculty of Medicine local ethic committee with the number 2024/195. and the study was conducted by the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients and control subjects.

Author Contributions

All authors received no financial support for the research, authorship, and/or publication of this article, Concept: S.C., M.K. Literature Review: S.C., M.K. Design: S.C., M.K. Data acquisition: S.C., M.K. Analysis and interpretation: S.C., M.K. Writing manuscript: S.C., M.K. Critical revision of manuscript: S.C., M.K.

Source of Finance

The authors declare that they have received no financial support for this study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Bronchoscopic-Guided Percutaneous Dilatational Tracheostomy: A Single-Center Experience

Barış Ecevit Yüksel[1], Ömer Zühtü Yöntem[1], Orhun Demir[1]

1 Department of Anesthesiology, Faculty of Medicine, Lokman Hekim University, Ankara, Türkiye

Abstract

Aim: Percutaneous dilatational tracheostomy (PDT) is a common procedure in intensive care units (ICUs) for patients requiring prolonged mechanical ventilation. This study aims to evaluate the outcomes of PDT under fiberoptic bronchoscopy guidance, comparing early versus late tracheostomy timing.

Methods: This retrospective study analyzed 57 patients who underwent PDT with fiberoptic bronchoscopy guidance. Patient demographics, Glasgow Coma Scale (GCS) scores, APACHE II scores, duration of mechanical ventilation, and complications were assessed.

Results: Of the 57 patients, 29.8% underwent early tracheostomy, and 70.2% underwent late tracheostomy. No significant differences were found in terms of age, gender, or GCS and APACHE II scores between the two groups. No significant differences in ICU length of stay, mortality, or weaning from ventilator were observed between the groups. The incidence of minor complications was similar between the two groups.

Conclusions: The study found no significant difference in clinical outcomes between early and late tracheostomy groups. While bronchoscopy enhanced procedural safety, it did not impact complication rates significantly. The timing of PDT should be individualized based on clinical judgment and patient condition. Tracheostomy timing should be tailored to each patient's condition, and larger studies are needed to define optimal timing guidelines.

***Keywords**: Percutaneous dilatational tracheostomy; fiberoptic bronchoscopy; mechanical ventilation; ICU; timing of tracheostomy*

1. Introduction

Percutaneous dilatational tracheostomy (PDT) is a commonly performed surgical procedure in intensive care units (ICUs) for patients receiving prolonged invasive mechanical ventilation. [1,2] Among the various PDT techniques, the percutaneous tracheostomy method described by Griggs and colleagues [3] is widely used, involving tracheal dilation with forceps to place the tracheostomy cannula.

The ability to perform PDT at the patient's bedside without the need for operating room transport, along with its lower complication rates, makes it widely used in ICU patients planned for elective tracheostomy. [4] However, complications can occur during and after the procedure, including bleeding, hypercapnia, hypoxia, subcutaneous emphysema, pneumothorax, sudden death, and esophageal injury. [5] Post-procedure complications may include early and late bleeding, pneumonia, stoma infection, cellulitis, tracheocutaneous fistula, and tracheoesophageal fistula. [5] The use of bronchoscopy during PDT can enhance procedural safety and reduce the incidence of complications both during and after the procedure. [6] Bronchoscopy helps to select appropriate incision site, to prevent posterior tracheal wall puncture and confirm the proper insertion of the cannula. However, it is still controversial to use bronchoscopy routinely when performing PDT. [7]

Bronchoscopy may facilitate PDT particularly in patients with limited neck extension. It was shown that very early (within 3 days) PDT under the guidance of bronchoscopy can be safely performed in anterior cervical spine fixation patients. [8]

Effects of timing of PDT on outcomes have been researched in literature and variable results have been achieved. In a retrospective study comparing very early versus early and late PDT in 255 ICU patients, it was found that very early tracheostomy achieved shorter length of hospital stay and reduced mortality. [9]

Clinical outcomes between trauma patients who underwent early (within 10 days), and late (after 10 days) tracheostomy were compared and early tracheostomy was found to reduce the length of hospital and ICU stay and duration of mechanical ventilation. [10]

Besides, a randomized controlled trial (RCT) showed no significant benefit for early (<10 days of intubation) versus late tracheostomy (>10 days of intubation). Additionally, it was found that only 45% of the cases who underwent to late tracheostomy actually needed it after 10 days. [11]

We aimed to retrospectively evaluate the clinical outcomes and

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complication rates in the patients who underwent early or late PDT performed under fiberoptic bronchoscopy guidance in our clinical practices in this study.

2. Materials and Methods

The study was carried out at the ICUs of Lokman Hekim University Ankara Hospital with a bed capacity of 51. The ethics committee approval was taken from the Lokman Hekim University Ethics Committee (Date: 29/11/2024, No: 2024/275). Data of the patients undergoing PDT in ICUs between January 2021 and October 2024 were obtained from the hospital database and analyzed retrospectively.

From the patient records, age, genders, ICU admission indications, Glasgow Coma Scale (GCS) scores, Acute Physiology and Chronic Health Evaluation-II (APACHE II) scores, duration of invasive mechanical ventilation (IMV) before and after tracheostomy, total duration of IMV, results of blood gas analyze results, early and late complications during and after tracheostomy were recorded.

2.1. Tracheostomy Procedure

From 2021 onward, tracheostomy procedures in our ICU have been performed bedside using bronchoscopy guidance, Griggs forceps for dilation, and a modified mini-surgical technique. After obtaining informed consent, pre-procedure evaluations of bleeding parameters and other laboratory tests were performed. If patients were under anticoagulants, appropriate adjustments were done. The PDT equipment was checked, and pre-oxygenation was provided with 100% FiO_2 with mechanical ventilator on a controlled mode. Patients were given adequate analgesia, sedation, and muscle relaxants. The preparation involved positioning the patient with transverse shoulder elevation to achieve head extension. After sterile cleaning of the surgical site and clothing, surgical asepsis was maintained with appropriate protective gear (cap, mask, sterile gown, and gloves) as well. The thyroid cartilage, the first, second, and third cricoid cartilages were marked with a marker. Local anesthesia (2% lidocaine with adrenaline) was applied at the identified site, followed by a vertical 1-1.5 cm incision. Bronchoscopy was used to visualize the trachea for guidance. Following vertical and transverse blunt dissection, mini-surgical exposure of the trachea was achieved. A needle attached to a 3-4 ml saline-filled syringe was inserted into the trachea and its position was verified via bronchoscopy and bubbles seen in the syringe when aspirated simultaneously. A J-tip guidewire was then introduced into the trachea, and dilation was performed using a small dilator followed by Griggs forceps over the guidewire. After ensuring hemostasis, the tracheostomy cannula was lubricated and inserted with the aid of the guidewire. Bronchoscopic visualization confirmed proper cannula placement, and lung ventilation was assessed using a stethoscope and by verifying mechanical ventilator settings. The endotracheal tube was removed, and the tracheostomy cannula was secured and dressed. Patients' admission diagnoses were categorized as neurological (cerebrovascular disease, degenerative and demyelinating diseases), infectious diseases, intracranial lesions, respiratory problems, post-cardiac arrest conditions, trauma, or cardiac-related events. Complications were classified as intra-procedural or post-procedural; intra-procedural complications included hypoxemia, acute bleeding, or death, while post-procedural complications included subcutaneous emphysema, bleeding, pneumothorax, stoma infection, and tracheal stenosis. Bleeding was classified as none, minor (controlled with sponges), moderate (requiring pressure dressing), or massive (requiring operating room intervention).

Table 1

Demographic data and ICU process of the patient groups receiving early and late tracheostomies

Variable	Total (n=57)	Early Tracheostomy (n=17)	Late Tracheostomy (n=40)	p
Male	30	10	20	0.5761
Female	27	7	20	
Age, years median (min;max)	74 (18-96)	60 (22-83)	75 (18-86)	0.3122
Duration from intubation to tracheostomy, days	13 (1-40)	7 (1-10)	19.5 (11-40)	<0.0013
After PDT MV days	13 (1-103)	10 (1-39)	13.5 (2-103)	0.4373
APACHE II	22.32 (±7.515)	22.12 (±6.224)	22.40 (±8.073)	0.8984
GCS	7 (3-15)	10 (3-15)	7 (3-15)	0.1503
Comorbidities of patients				
· Hypertension	32	6	26	0.0381
· Diabetes mellitus	23	7	16	0.5811
· Chronic obstructive pulmonary disease	14	2	12	0.1281
· Asthma	1	0	1	0.7021
· Cardiovascular disease	27	7	20	0.3751
· Malignancy	6	2	4	0.5861
· Chronic renal disease	3	0	3	0.3381
· Cerebrovascular disease	8	1	7	0.2381
Admission diagnoses				
· Neurological	4 (7%)	0 (0%)	4 (10%)	
· Infection	8 (14%)	3 (17.6%)	5 (12.5%)	
· Intracranial lesions	6 (10.5%)	2 (11.8%)	4 (10%)	
· Respiratory	24 (42.1%)	7 (41.2%)	17 (42.5%)	
· Post-CPR	4 (7%)	0 (0%)	4 (10%)	
· Trauma	1 (1.8%)	1 (5.9%)	0 (0%)	
· Cardiac	10 (17.5%)	4 (23.5%)	6 (15%)	

APACHE II: Acute physiology and chronic health evaluation-II scores; GCS: Glasgow Coma Scale; MV: Mechanical ventilation; Cardiopulmonary resuscitation CPR; Percutaneous dilatational tracheostomy PDT; 1: Fisher's Exact test; 2: Pearson chi-square test; 3: Mann–Whitney U test; 4: Student's t-test

Table 2

Respiratory parameters of early and late tracheostomy groups on the admission day

Variable	Total (n=57)	Early Tracheostomy (n=17)	Late Tracheostomy (n=40)	p
Admission Day				
· pH	7.38 (6.82-7.56)	7.38 (7.27-7.54)	7.37 (6.82-7.56)	0.5621
· PaCO2, mmHg	41 (21-219)	40 (26.3-81.8)	41.1 (21-219)	0.8621
· PaO2, mmHg	65.8 (21.6-242)	60 (40-169)	71.5 (21.6-242)	0.4221
· PaO2/FiO2	131 (43-484)	120 (80-338)	143 (43-484)	0.4271
Tracheostomy Day				
· pH	7.45 (7.04-7.77)	7.44 (7.12-7.60)	7.47 (7.04-7.77)	0.2711
· PaCO2, mmHg	39 (20-77)	42 (28-60)	37 (20-77)	0.1931
· PaO2, mmHg	94 (41-165)	65 (41-126)	102 (49-165)	0.0091
· PaO2/FiO2	188 (82-330)	130 (82-252)	204 (98-330)	0.0091

FiO2: Fraction of inspired oxygen; PaCO2: Arterial partial pressure of carbon dioxide; PaO2: Arterial partial pressure of oxygen; 1: Mann–Whitney U test

Table 3

Outcomes of critically ill patients receiving early and late tracheostomies

Variable	Total (n=57)	Early Tracheostomy (n=17)	Late Tracheostomy (n=40)	p
Mortality	43 (75.4%)	12 (70.6%)	31 (77.5%)	0.3081
ICU LOS, days	35 (7-153)	35 (13-81)	35 (7-153)	0.8962
Hospital LOS, days	40 (8-153)	42 (13-81)	40 (8-153)	0.8822
Weaning success	14 (24.6%)	5 (29.4%)	8 (22.5%)	0.4053
Discharge	12 (21%)	4 (23.6%)	8 (20%)	0.6421

ICU: Intensive care unit; LOS: Length of stay; 1: Pearson chi-square test; 2: Mann–Whitney U test; 3: Fisher's Exact test

2.2. Statistical Analysis

Statistical analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) version 27.0 program. Shapiro-Wilk test, histogram, and skewness-kurtosis coefficients were used to evaluate normal distribution of the data. For the variables distributed normally the Student's T-test and for parameters that did not have a normal distribution Mann-Whitney U test was used when comparing paired groups. To evaluate Multivariate cross-tabulations Fisher's Exact test or Chi-square test were used. The survival analysis was evaluated using Kaplan-Meier analysis in groups. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Features of the overall group

A total of 57 patients were included in the study. The median age of the patients was 74 years (range: 18-96), and 30 patients (52.6%) were male. The median number of days on positive pressure mechanical ventilation before the tracheostomy procedure was 13 days (range: 1-40). The median duration of follow-up with tracheostomy was 18 days (range:2-150), the median ICU length of stay was 35 days (range:7-153) and the median hospital length of stay was 40 days (range:8-153). The mean APACHE II score of all patients was 22.32 (±7.515), and the median GCS score was 7 (range: 3-15). Hypertension was the most common comorbidity (56.1%), followed by heart disease in 47.4% of cases, diabetes mellitus in 40.4%, and chronic obstructive pulmonary disease (COPD) in 24.6%. When examining hospital admission diagnoses, 42.1% were respiratory, 17.5% cardiac, 14% infection, 10.5% intracranial lesions, 7% post-CPR, 7% neurological, and 1.8% trauma. There was no statistical difference in terms of admission diagnoses between groups (p=0.368). Demographic data and ICU process of the patients undergoing early and late tracheostomies are shown in **Table 1**.

Of 57 cases, 43 patients (75.4%) died during intensive care follow-up. The overall success rate of weaning from the ventilator was 24.6%.

3.2. Comparison of the early and late tracheostomy groups

PDT performed within 10 days of intubation was defined as early PDT and PDT performed after more than 10 days of intubation was defined as late PDT according to existing literature. Patients were then divided into two groups; Seventeen (29.8%) of 57 patients were classified in the early group, and 40 patients (70.2%) were classified in the late group. The early and late groups were similar in terms of age and gender, with no statistical difference observed. The median number of days on positive pressure mechanical ventilation before the tracheostomy procedure was 7 days (range: 1-10) in the early group, and 19.5 days (range: 11-40) (p<0.001) in the late group. There was no difference in terms of APACHE II and GCS scores between the early and late groups. Among comorbidities, only hypertension showed a marginally significant difference between groups (p=0.038).

Comparing arterial blood gas values on the first day of admission, early and late tracheostomy groups were found similar. Arterial blood gas values on the tracheostomy day were compared as well; PaO_2 (mmHg) was 65 (range:41-126) in the early tracheostomy group and 102 (range:49-165) in the late tracheostomy group, showing a statistically significant difference (p = 0.0091). PaO_2/FiO_2 ratio was 130 (range:82-252) in the early tracheostomy group and 204 (range:98-330) in the late tracheostomy group, also demonstrating a statistically significant difference (p = 0.009) (**Table 2**).

Complications during the procedure included hypoxemia in 1 patient (1.8%) in the overall group, with 2.5% in the late tracheostomy group. Acute bleeding occurred in 4 patients (7%), with 1 patient (5.9%) in the early tracheostomy group and 3 patients (7.5%) in the late tracheostomy group. Post-procedural

complications included subcutaneous emphysema in 1 patient (1.8%), with 1 patient (5.9%) in the early tracheostomy group and none in the late tracheostomy group. Minor bleeding was observed in 3 patients (5.3%), with none in the early tracheostomy group and 3 patients (7.5%) in the late tracheostomy group. No moderate bleeding, pneumothorax, or tracheal stenosis were observed in any of the groups. Stoma infection occurred in 1 patient (1.8%), with none in the early tracheostomy group and 1 patient (2.5%) in the late tracheostomy group.

Twelve (70.6%) of 17 patients in the early group died in ICUs. while 31 (%77,5) patients died in the late group. The median ICU stay was 35 days (range: 13-81) for the early group and 35,5 days (range: 7-153) for the late group, with no statistically significant difference (p>0.05). The success rate of weaning from the ventilator was slightly higher with an incidence of 29.4% in the early tracheostomy group when compared to late tracheostomy group (22.5%), though the difference was not statistically significant (**Table 3**). A total of 4 (7,0%) patients, 3 of them in early and 1 in late tracheostomy group were decannulated during ICU stay.

Univariate and multivariate regression analysis was performed for variables that may have influenced PTD timing. None of the parameters were found to be an independent influencing factor for timing of PDT. Regression analysis of variables that may influence PDT timing is shown in **Table 4**.

Table 4

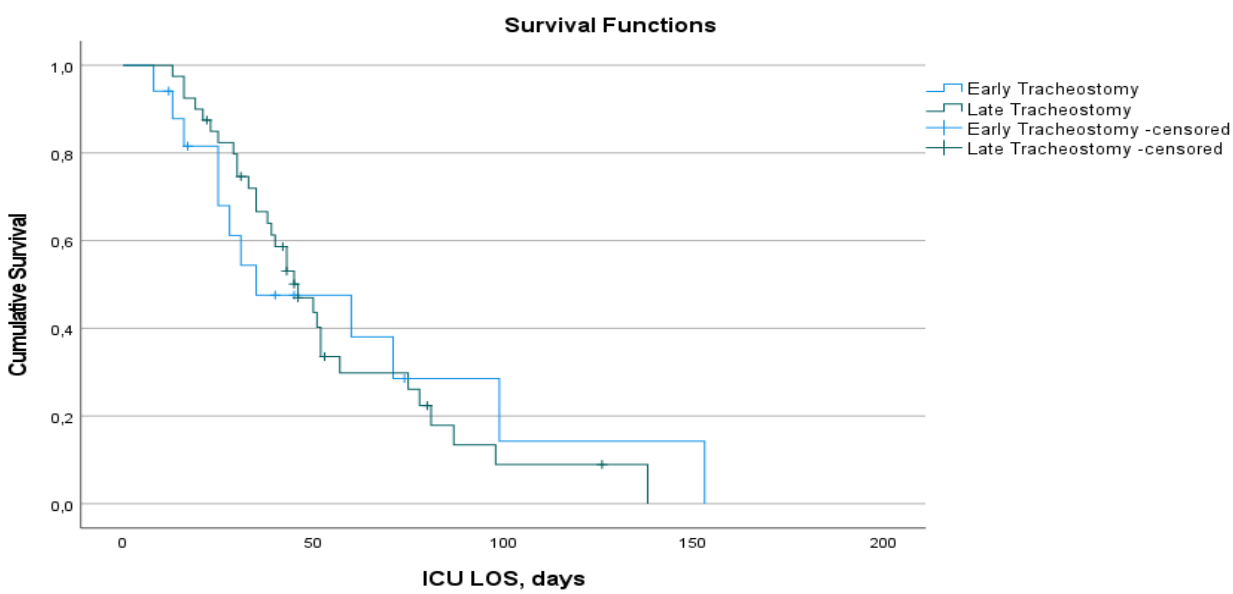
Regression analysis of variables that may influence PDT timing

Variables	Univariate binary logistic regression				Multivariate binary logistic regression			
	p	Exp(B)	95% C.I.for EXP(B) Lower	Upper	p	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Age	0.021	1.040	1.006	1.075	0.114	1.030	0.993	1.069
GCS (≥8, <8)	0.151	2.337	0.733	7.451				
APACHE II	0.896	1.005	0.931	1.085				
Hypertension	0.043	3.405	1.038	11.171	0.301	0.488	0.125	1.903
Diabetes Mellitus	0.934	1.050	0.331	3.331				
Chronic obstructive pulmonary disease	0.159	0.311	0.061	1.577				
Asthma	1	0	0					
Heart failure	0.542	0.700	0.222	2.206				
Malignancy	0.843	1.200	0.198	7.267				
Chronic renal disease	0.999	0	0					
Cerebrovascular disease	0.272	0.295	0.033	2.603				

APACHE II: Acute physiology and chronic health evaluation-II scores; GCS: Glasgow Coma Scale;

Figure 1

Comparison of Survival Rates in Early and Late Tracheostomy Patients Using Kaplan–Meier (P-log-rank: 0.860).



Kaplan–Meier analysis for survival was performed. Hazard ratio was found to be 0,892 (CI; 0,449-1,771) reflecting a 10,8% lower mortality rate in early PDT group but was not statistically significant (p = 0.744). Kaplan-Meier survival analysis for early and late tracheostomy patients is presented in **Figure 1**. The median survival time was 35 days for the early tracheostomy group and 46 days for the late tracheostomy group. The difference was not statistically significant (P-log-rank = 0.860).

4. Discussion

The clinical outcomes of early and late tracheostomy in ICU patients undergoing PDT were evaluated in this study.

In our study, no statistically significant difference was found between the early and late groups regarding total length of stay in the ICU. In a randomized controlled trial (RCT) involving stroke patients monitored in the intensive care unit, patients were grouped into early (1-3 days) and standard (7-14 days) tracheostomy timing groups; length of ICU stay was found similar between the groups, but mortality was lower in the early group compared to the standard group. [12] A meta-analysis identified a lower mortality rate in the early tracheostomy group (<10 days) compared to the late tracheostomy group as well. [13] It was found in a publication investigating 127,475 tracheostomy patients' data obtained from The National Inpatient Survey found that early tracheostomy reduces mortality, medical care at home, length of stay in the ICU, and overall hospital costs. [14]

No statistically significant difference was found in mortality between the early and late tracheostomy groups in our study. The success rate of weaning from the ventilator was slightly higher in the early tracheostomy group when compared to late tracheostomy group but was not statistically significant.

In a recent publication comparing surgical tracheostomy and PDT, PDT resulted in significantly decreased long-term follow up, delayed decannulation and increased complications. They concluded that protocols of PDT in the ICU need to be refined. [15]

We could not evaluate the long-term complication rates because of the inability to reach the long-term follow-up records of the patients but we have observed a relatively low complication rate with PDT in our study.

In the literature the incidence of complications during PDT varies for each complication; for pneumothorax 0-4 %, for sub-cutaneous emphysema 0-4 %, for stomal infection 0-10 %, for hypoxia 0-25 %.

In a prospective randomized study comparing conventional and semi-surgical PDT it was found that the incidence of hypoxemia, intraoperative bleeding, pneumomediastinum, pneumothorax, subcutaneous emphysema and stoma infection was 0% during semi surgical PDT. They found an incidence of 1,3% for postoperative bleeding and loss of airway. They have concluded that semi-surgical PDT is associated with lower complication rates when compared to conventional PDT. [16]

We have observed hypoxemia in 1.8%, acute bleeding in 7%, subcutaneous emphysema in 1.8%, minor bleeding in 5.3% and stoma infection in 1.8% of the overall population. Moderate bleeding, pneumothorax, or tracheal stenosis were not observed in any of the patients in our study. Though our complication rates were similar with the existing literature and relatively low probably because of semi surgical PDT technique, comparison of the early and late PDT in terms of complications may not be powerful due to relatively smal sample size.

Fiberoptic bronchoscopy facilitates better visualization of airway structures, potentially reducing injuries and enhancing procedure safety during tracheostomy. While its use may minimize complications, retrospective analyses demonstrated that bronchoscopy did not affect complication rates significantly. [17,18] One study reported no difference in complication rates between patients who underwent PDT with and without bronchoscopy. However, comparing these groups was challenging as patients undergoing bronchoscopy often presented with technically more complex situations. [17] Similarly, another retrospective review found no impact of bronchoscopy on the complication rates. [18] In a study of PDT performed using the Griggs technique without guidance of a bronchoscopy, complication and mortality rates were reported as 8.6% and 0.6% respectively, concluding that PDT without guidance of a bronchoscopy is safe. [19] Other studies have reported lower complication rates; one indicated a 3.5% complication rate, while another reported a 0.17% mortality rate. [20,21] Despite limited data supporting its use, bronchoscopy during PDT remains common practice. A survey by Kluge et al. [22] demonstrated that 98% of ICUs in Germany routinely use bronchoscopy during PDT. The incidence of complications was relatively low in our study; the complication rate during the PDT procedure was found to be 7.8%, and in the post-procedure period, it was 8.9%.

In a multicenter randomized controlled trial conducted across 70 general ICUs and 2 cardiothoracic ICUs in the United Kingdom between 2004 and 2011, 91.9% of patients in the early tracheostomy group underwent the procedure as planned, whereas only 45.5% of patients in the late group required tracheostomy. Many late group patients were weaned off mechanical ventilation without needing tracheostomy. This study documented the limited capability of the physicians to predict which cases will need prolonged ventilatory support. These findings highlight that individual clinical conditions should guide tracheostomy timing and emphasize the importance of a patient-centered approach. [23]

Findings of our study suggest that tracheostomy timing does not significantly impact mortality. The decision between early and late tracheostomy is complex and requires a dual approach: first, predicting which cases will need longer duration of mechanical ventilation, and second, determining the optimal timing for tracheostomy. If the prediction of prolonged ventilation needs is inaccurate, an early tracheostomy strategy may lead to redundant procedures for some patients, while a late strategy may expose others to unnecessarily prolonged endotracheal intubation.

4.1. Study Limitations

One of the major limitations of this study is its retrospective design. The lack of randomization when enrolling the patients into early and late groups is also a weak point because the decision to perform early or late tracheostomy was given upon the clinicians' opinion or permission of the patients' relatives. The severity of the disease or survival expectancy of the patient could have affected the clinicians 'decision on timing of PDT and these issues may have resulted in a selection bias. Another weak point of the study is its relatively small sample size which could have led to a type II error and failure to detect a true difference. Lastly, the lack of knowledge regarding long-term outcomes is another limitation.

5. Conclusion

As a conclusion, the timing of percutaneous tracheostomy and performing it either under guidance of fiberoptic bronchoscopy or not should be tailored to the patient's overall clinical condition and individual needs. Although the timing of tracheostomy appears to be determined by the physician's clinical intuition and experience, it is essential to prioritize a patient-centered, individualized approach and clearer tracheostomy timing algorithms should be de-

veloped through larger-scaled and randomized controlled prospective clinical trials.

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Statement of ethics

Ethical approval was obtained from the Lokman Hekim University Ethics Committee (Date: 29/11/2024, No: 2024/275) and the study was conducted by the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients and control subjects.

Source of Finance

The authors declare that they have received no financial support for this study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Rosmarinic Acid Alleviated Cyclophosphamide Induced Gonadal Toxicity in Adult Male Rats

Fırat Şahin[1], Engin Deveci[1], Fırat Aşır[1],
Merve Gülsen Bal Albayrak[2], Ebru Gökalp Özkorkmaz[3]

1 Dicle University, School of Medicine, Department of Histology and Embryology, Diyarbakir, Türkiye
2 Department of Medical Biology, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye
3 Ankara Yıldırım Beyazıt University, Faculty of Health Sciences, Ankara, Türkiye

Abstract

Aim: This study aimed to investigate the potential protective effects of rosmarinic acid (RA) against cyclophosphamide (CP)-induced gonadal toxicity in male Wistar Albino rats. Specifically, the research focused on the modulation of apoptotic pathways, with an emphasis on Bax protein expression, and utilized bioinformatic analyses to elucidate the key molecular mechanisms and signaling pathways underlying the observed effects.

Methods: The experimental design consisted of four groups: Control (administered saline), RA (administered rosmarinic acid), CP (administered cyclophosphamide), and RA+CP (administered a combination of rosmarinic acid and cyclophosphamide). Following a 14-day treatment period, body weight, serum malondialdehyde (MDA) levels, and Bax protein expression in testicular tissue were evaluated. Additionally, a protein-protein interaction (PPI) network influenced by RA and CP was constructed using STITCH and subsequently analyzed in Cytoscape. Functional enrichment analysis was performed to identify key molecular pathways associated with Bax regulation, with an emphasis on clusters exhibiting significant associations ($p < 0.05$) for enhanced interpretability.

Results: In the CP group, a significant reduction in body weight was observed, alongside elevated serum malondialdehyde (MDA) levels, indicative of heightened oxidative stress, and increased Bax protein expression, reflecting enhanced apoptotic activity. In contrast, the RA+CP group exhibited preservation of body weight, reduced Bax expression, and lowered MDA levels, closely resembling the profiles of the control group. Bioinformatic analyses revealed that CP predominantly activated molecular pathways associated with oxidative stress, apoptosis, and lipid metabolism. In comparison, RA treatment modulated pathways involved in mitochondrial protection, endoplasmic reticulum (ER) stress response, and the regulation of cytochrome c release, highlighting its potential protective role.

Conclusions: This study demonstrates that the antioxidant and anti-inflammatory properties of rosmarinic acid (RA) significantly mitigate cyclophosphamide (CP)-induced gonadal toxicity in male rats. The protective effects of RA are evident in its ability to preserve body weight, reduce oxidative stress, and suppress Bax protein expression, a key marker of apoptosis. Furthermore, in-silico analyses confirm that RA exerts its protective effects by modulating critical apoptotic pathways, specifically through the inhibition of Bax expression and the reduction of oxidative stress. These findings underscore the potential of RA as a therapeutic agent to prevent CP-induced gonadal damage, offering promise for its future application in protecting against chemotherapy-related reproductive toxicity.

Keywords: *Bax expression; cyclophosphamide; gonadal toxicity; rosmarinic acid.*

1. Introduction

Cyclophosphamide (CP) stands out as a highly successful anticancer drug, continuing to be utilized even 50 years after its synthesis. Widely employed in chemotherapy, blood, and bone marrow transplantation procedures, CP exhibits a broad range of clinical applications[1]. Despite its efficacy, CP is associated with reproductive toxicity in both humans and experimental animals[2]. Adverse effects include reduced gonad weight, impaired spermatogenesis, azoospermia, oligospermia, and significant abnormalities in the repro-

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ductive system[3]. Histological changes, particularly in the seminiferous tubule epithelium, have been observed following CP exposure, which may lead to degeneration and cell losses in spermatogenesis[4]. The exact cause of CP-induced gonadal toxicity remains unclear, but studies indicate that severe oxidative and nitrative stress, inflammation, apoptosis, and genomic changes play pivotal roles. Long-term exposure to CP has been linked to male infertility, various reproductive dysfunctions, and oncogenic effects[5]. The therapeutic and toxic effects of the drug are primarily dependent on hepatic metabolism, where the cytochrome P450 mixed-function oxidase system generates active metabolites, including phosphoramide mustard and acrolein[6]. Elangovan et al. have reported that the administration of a high dose of cyclophosphamide to the testes may lead to permanent functional impairments[7]. Natural antioxidants, like Rosmarinic Acid (RA), found in plants of the Lamiaceae family, have demonstrated potential in reducing CP toxicity. RA acts as a free radical scavenger, exhibiting antiviral, antibacterial, and immunomodulatory properties[8,9]. RA is widely used in food preservation, cosmetics, and the medical field due to its antimicrobial and antioxidant activities. Experimental studies indicate RA's protective effects in conditions such as Alzheimer's, wound healing, and renal ischemia-reperfusion damage[10,11]. Additionally, RA has been shown to significantly increase serum testosterone levels in rats, emphasizing its potential impact on reproductive functions[12,13].

In conclusion, cyclophosphamide (CP)-induced gonadal toxicity remains a significant clinical concern, prompting the investigation of antioxidants, particularly rosmarinic acid (RA), as potential mitigators of these adverse effects. This study aims to provide a comprehensive evaluation of RA's protective role against CP-induced reproductive toxicity, with a particular emphasis on histological alterations and functional impairments in the male reproductive system. By exploring RA's potential to counteract CP-induced gonadal damage, this research seeks to contribute valuable insights that may guide the development of therapeutic strategies to alleviate the reproductive side effects associated with CP treatment.

2. Materials and Methods

2.1. Experimental design

The Animal Ethics Committee approval, designated as 2020/16, was secured from the local ethics committee of Dicle University. Male Wistar Albino rats, aged 15-16 weeks and weighing between 200-240 grams, were obtained from the Dicle University Health Sciences Research and Application Center for the study. The study divided into four groups: Control (n=7), Rosmarinic Acid (RA, n=7), Cyclophosphamide (CP, n=7), and Rosmarinic Acid + Cyclophosphamide (RA+CP, n=7). The rats were housed in stainless steel cages under controlled conditions, maintaining a 12-hour light/dark cycle at a temperature of 22±2°C. Throughout the study, the rats had unrestricted access to both water and food. The experimental procedure lasted for 14 days, involving daily intraperitoneal injections. Comprehensive assessments through immunohistochemical and Western blot examinations. Additionally, biochemical analyses were conducted following specific protocols, ensuring a rigorous and consistent methodology throughout the study. The experimental design and durations were adapted from Alami et al.[14] and Sabik et al.[8] for consistency and referencing within the scientific literature.

2.2. Malonaldehyde (MDA) level analysis

MDA, a byproduct of cellular polyunsaturated fatty acid peroxidation, serves as an oxidative stress indicator. Post-experiment, rat blood samples underwent centrifugation, and plasma was stored at -80°C for subsequent MDA analysis. Thawed plasma was mixed with TCA and TBA, heated, and spectrophotometrically read at 532 nm. MDA values, calculated using extinction coefficients and dilution factors, underwent statistical analysis in SPSS 24.0, employing Anova and Post-Hoc Tukey and Games-Howell tests ($p \leq 0.05$).

2.3 Tissue processing for immunohistochemical staining

After sacrifice, rat testicular tissues underwent fixation in 10% neutral buffered formaldehyde (Catalog no: HT501128, 4L, Sigma, Germany) for 6 hours, followed by an additional 18 hours in clean neutral formalin. Post-fixation, tissues were rinsed in tap water for 12 hours to eliminate excess formalin. Sequential dehydration occurred in 50%, 70%, 80%, 90%, and 96% ethanol baths for 8 hours, concluding with a final step of 2x30 minutes in absolute alcohol. To remove residual alcohol, tissues underwent 2x15 minutes of xylene treatment. For infiltration, tissues were incubated in molten paraffin at 58°C for 3x30 minutes in an oven. Paraffin-embedded tissue blocks were then embedded at room temperature, and 5 µm thick sections were obtained using a Leica R52265 rotary microtome, mounted on positively charged slides. Sections were incubated in xylene for 15 minutes in two consecutive series, followed by treatment with decreasing alcohol concentrations (100%, 90%, 80%, 70%) for 5 minutes each. After a 2x15 minute distilled water rinse, sections underwent a 3-minute antigen retrieval process in EDTA solution at 90°C using a microwave. Post-microwave, sections were incubated in Phosphate Buffer Saline (PBS) at room temperature for 20 minutes. Hydrogen peroxide block solution was applied for 20 minutes, followed by 2x5 minute PBS washes. Ultra V Block solution was then applied for 8 minutes. Subsequently, Bax primary antibody (Thermo fisher/PA5120029) was applied overnight at 4°C. The next day, sections were left at room temperature for 1 hour, followed by 2x5 minute washes. After washing, sections were incubated with a secondary antibody for 14 minutes. Following 2x5 minute PBS washes, sections underwent enzyme binding with Streptavidin peroxidase for 15 minutes. Further washes were performed, and sections were subjected to a DAB chromogen reaction. Specific reaction sections were collected in PBS, followed by counterstaining with Mayer's hematoxylin, dehydration, xylene treatment, and mounting with Entellan. Prepared slides were examined using a Zeiss Imager A2 light microscope and Zen 3.00 software.

2.4. Western blot protocol

Testicular tissue lysates, frozen at -80°C, were processed for protein analysis using the Smart BCA assay. In the Western blot laboratory, resolver and stacker gels were prepared with the TGX Stain-Free™ FastCast™ Acrylamide Solution. Protein samples were loaded onto these gels for electrophoresis. Following gel electrophoresis, proteins were transferred onto a PVDF membrane. Subsequent steps, including antibody incubation and imaging, were carried out using the Bio-Rad ChemiDOC MP system.

2.5. Statistical analysis and Bioinformatics Approaches

Rat weights were measured pre-experiment, and post-experiment weight checks were conducted for rats receiving the appropriate dose (mg/kg). Prior to the experiment, rat weights were measured. Prior to the experiment, rat weights were measured. Following administration of the appropriate dose (mg/kg), post-experiment weight assessments were conducted.

Statistical analysis was done using the IBM SPSS 25.0 software (IBM, Armonk, New York, US). The data were recorded as median (minimum-maximum). Normality of the data distribution was evaluated with the Shapiro-Wilk test. Group comparisons were done with the Kruskal Wallis and post hoc Mann- Whitney U test. Significance was considered for $p \leq 0.05$. The number of animals for each group was calculated by G Power analysis (version 3.1).

3. Results

3.1 Statistical Findings and Bioinformatics Findings in Evaluating Toxicity

In the pre-experiment phase, rat body weights were measured, and doses were administered. Post-application, body weights were re-measured. The control group showed no significant difference in weights before (237±11.02 g) and after (232±14.07 g) the experiment (p>0.05). The RA group also exhibited no significant difference in weights before (211±7.02 g) and after (204±10.03 g) the experiment (p>0.05). However, the CP group displayed a significant difference in weights before (207±3.02 g) and after (149±11.02 g) the experiment (p≤0.01), indicating a significant decrease. In contrast, the RA+CP group showed no significant difference in weights before (213±5.02 g) and after (199±13.09 g) the experiment (p>0.05). CP significantly decreased the animal's weight, but RA treatment mitigated this effect, helping to maintain the animal's wellbeing (**Fig. 1.**and **Table 1.** show the results).

Average animal weights before and after the experiment were shown in **Table 1**. A significant decrease in animal weight is observed following the administration of CP. However, in the RA+CP group, the RA treatment mitigates this weight loss, preventing significant reductions in body weight.

Figure 1

Graphical representation illustrates the variations in animal weights before and after the initiation of the experiment. The chart presents a comparative analysis of the average weights of rats within each group, both prior to and following the experimental intervention.

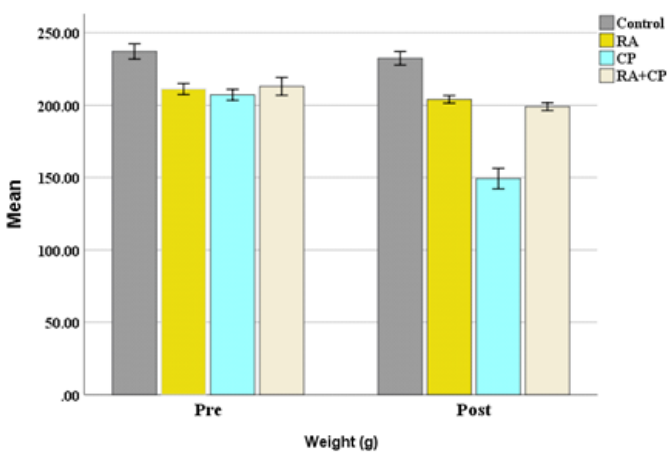


Table 1

Pre and post experiment animal weights

Groups	Pre-experiment	Post-Experiment	p
Control	237±11.02	232±14.07	0.067
RA	211±7.02	204±10.03	0.081
CP	207±3.02	149±11.02	0.001
RA+CP	213±5.02	199±19.09	0.002

3.2. MDA Analysis

Serum Malondialdehyde (MDA) concentrations in rats were measured as follows: 1.2 ± 0.03 nmol/ml for the control group, 1.3 ± 0.2 nmol/ml for the RA group, 2.5 ± 0.9 nmol/ml for the CP group, and 1.7 ± 0.03 nmol/ml for the CP+RA group. The difference in MDA levels between the control and RA groups was not statistically significant (p>0.05). However, a significant increase was observed in the CP group compared to the control group (p≤0.01). Additionally, there was a statistically significant reduction in MDA levels in the RA+CP group compared to the CP group (p<0.05). MDA levels increased after CP induction compared to the control group, but RA treatment significantly reduced MDA concentrations compared to the CP group (**Fig. 2.** and **Table 2**).

3.3 Immunohistochemical findings.

Examination of Bax immune stained testicular sections were show in in **Figure 4**. Control and RA group showed negative Bax expression in the seminiferous tubules, spermatogonia and spermatid cells (**Fig. 3a** and **3b**, respectively). In the CP group, positive Bax expression was observed in spermatogenic cells and in interstitial cells (**Fig. 3c**). In the RA+CP group, Bax expression was reduced in the seminiferous tubule structures. Bax expression was negative in Sertoli cells and in the interstitial connective tissue areas (**Fig. 3d**).

Figure 2

Graphical representation of Serum Malondialdehyde (MDA) concentrations by Group.

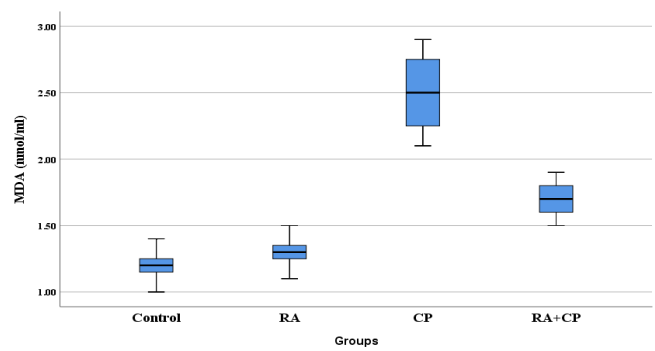


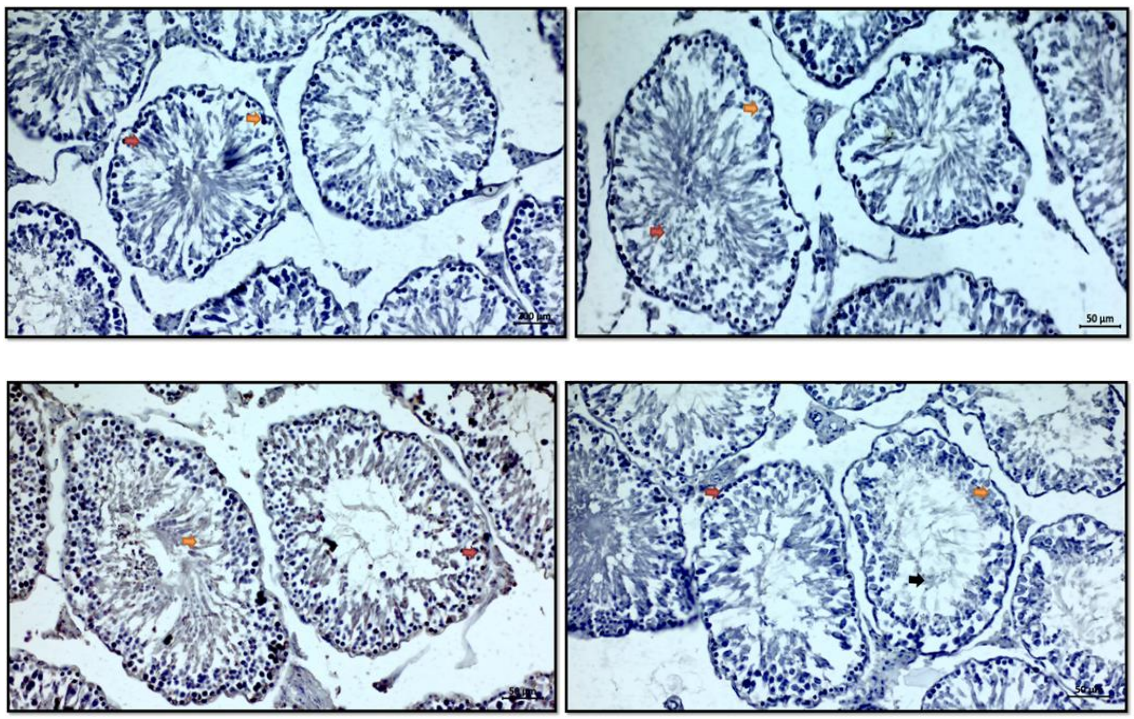
Table 2

The MDA values for each group. Following CP induction, MDA levels increased compared to the control group. However, RA treatment significantly reduced MDA content in comparison to the CP group (* Control vs CP, **CP vs RA+CP).

Groups	MDA (nmol/ml)	p
Control	1.2 ± 0.03 (1.0-1.4)	
RA	1.3 ± 0.2 (1.1-1.5)	
CP	2.5 ± 0.9 (2.1-2.9)	0.002*
RA+CP	1.7 ± 0.03 (1.5-1.9)	0.001**

Figure 3

Bax immunostained testicular sections.



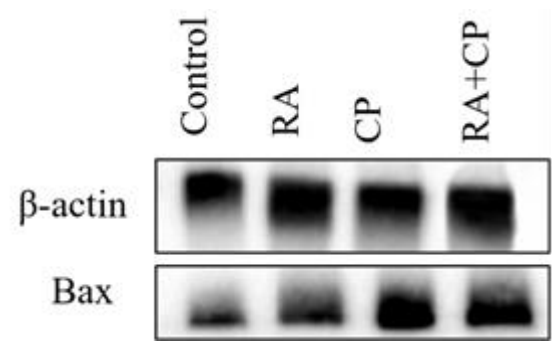
A) *Control group, negative Bax expression in spermatogonia cells (orange arrow) and spermatid cells (red arrow),*
B) *RA group, negative Bax expression in Sertoli cells (orange arrow) and spermatid cells (red arrow);*
C) *intense Bax expression in spermatogonia cells (red arrow) and spermatid cells (orange arrow);*
D) *CP+RA group, negative Bax expression in spermatogonia cells (red arrow) and spermatid cells (black arrow). Bax immunohistochemistry; Scale bar: 50 µm*

3.4. Western Blot Results

Protein bands of Bax in testicular tissues per group was visualized in **Figure 4**. β-Actin was used as a positive control. The CP group showed a significantly increased band thickness compared to the control group and RA group, indicating elevated Bax expression. In the comparison of Bax expression between the CP and RA+CP groups, the CP group demonstrated higher Bax levels, whereas Bax protein levels were notably down-regulated in the RA+CP group. These findings suggest that CP treatment leads to increased Bax expression, as evidenced by the thicker bands, while RA+CP treatment results in reduced Bax expression. (**Fig. 5.**). Bioinformatic analyses revealed that CP primarily activated pathways related to oxidative stress, apoptosis, and lipid metabolism, all critical to chemotherapy-induced damage. Specifically, pathways such as "oxidation by cytochrome P450," "apoptosis," and "response to oxidative stress" were significantly enriched upon CP-treatment (**Figure 5.-A**). Conversely, RA treatment predominantly influenced pathways related to mitochondrial protection, ER stress response, and regulation of cytochrome c release from mitochondria, including "regulation of release of cytochrome c," "response to hypoxia," and "ER stress response." (**Figure 5**).

Figure 4

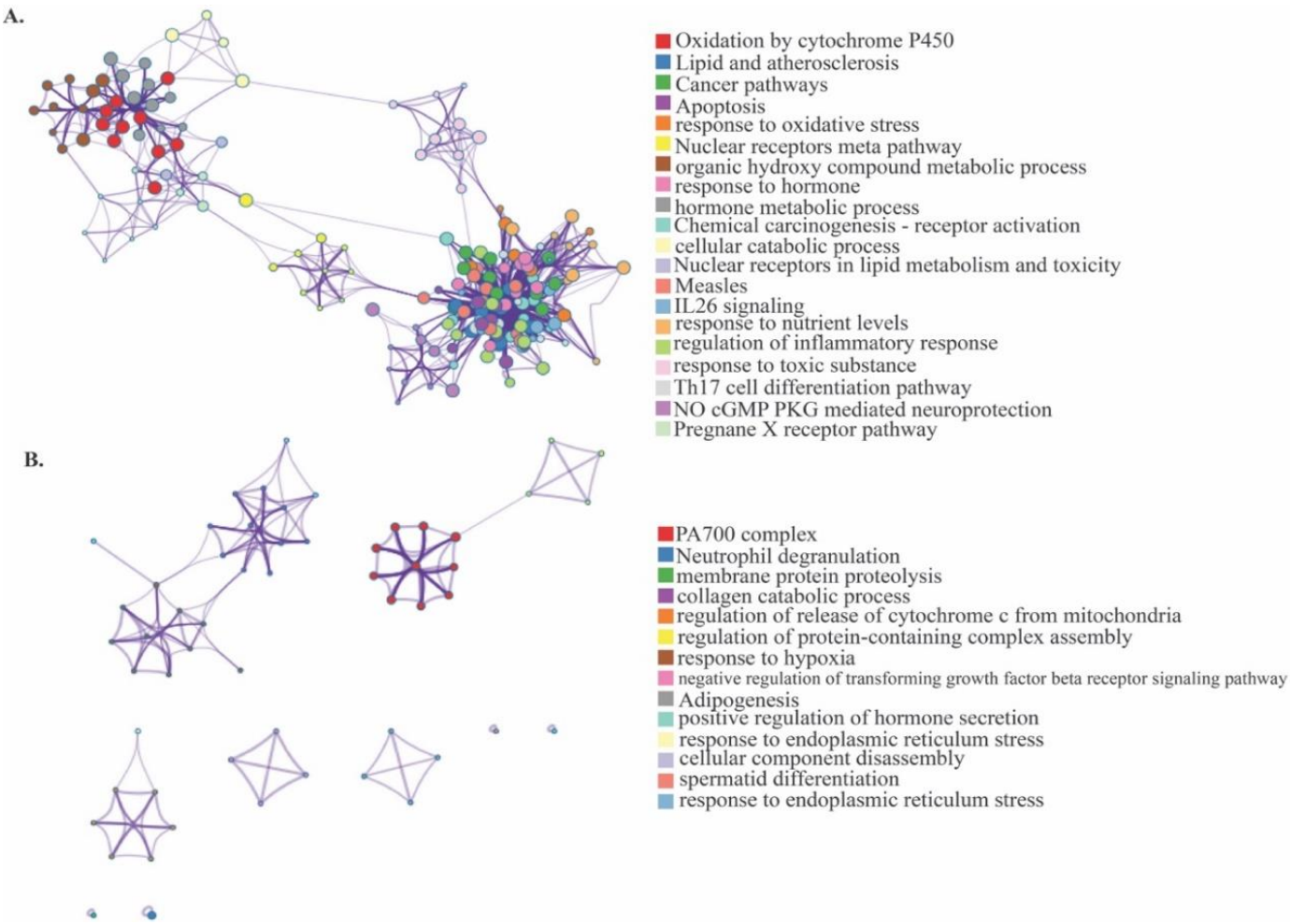
Bax Protein Levels Across Groups



In the CP group, there was a significant increase in Bax protein levels compared to the control group and RA group. RA treatment decreased Bax band intensity in the RA+CP group.

Figure 5

Protein-protein interaction (PPI) network and functional enrichment analysis of genes affected by Cyclophosphamide (CP) and Rosmarinic Acid (RA). A. PPI network of CP-affected genes and the top 10 statistically significant pathways influenced by CP. B. PPI network of RA-affected genes and the top 10 statistically significant pathways influenced by RA. Pathway annotations are listed from top to bottom in order of increasing p-values. Statistical significance was set at $p < 0.05$.



4. Discussion

The Cyclophosphamide (CP), a phosphoramide phosphoramide mustard derivative, is a widely used alkylating agent known for its antineoplastic and immunosuppressive properties. It is commonly administered alongside other chemotherapeutic agents in the treatment of various cancers such as malignant lymphomas, breast cancer, ovarian carcinoma, and myeloblastoma. Additionally, CP is employed in immunosuppressive therapy to prevent graft rejection and treat chronic autoimmune disorders, including rheumatoid arthritis and myasthenia gravis. CP acts by interfering with cell growth and differentiation, particularly affecting rapidly proliferating tissues like the gonads. While effective as a therapeutic agent, it also has notable toxic effects on various organs and tissues. At high doses (greater than 50 mg), over 65% of patients experience nausea and vomiting within approximately 12 hours of administration. Between 5% and 30% of patients undergoing CP treatment experience significant hair loss. Experimental studies in animal models have also confirmed CP's toxicity and teratogenicity, indicating its adverse effects on fetal development. In patients, CP can induce cystitis, with the incidence of this condition increasing with the dosage. CP, along with cumulative dosage and patient age, is also associated with an increased risk of early menopause in women and infertility in men. Pathological examinations reveal ovarian atrophy, fibrosis, and complete absence of follicular structures as key histological features in women. In men, prolonged CP treatment can result in irreversible azoospermia, with significant degeneration of seminiferous tubules and Sertoli cells, signaling extensive gonadal damage. In some cases, CP treatment in women leads to irreversible amenorrhea[15-17]. Trasler et al. evaluated the effects of cyclophosphamide (CP) on male Sprague-Dawley rats by administering low (5.1 mg/kg/day) and high doses (6.8 mg/kg/day) for up to 9 weeks. Sig-

nificant reproductive toxicity was observed, with oligospermia and azoospermia detected at both doses after 6 weeks. Histological and biochemical analyses confirmed substantial testicular damage, emphasizing the detrimental impact of CP on male fertility[18]. Hoorweg-Nijman et al. examined 23 male patients (ages 14.8–28.8) and found that cyclophosphamide (CP) treatment disrupted gonadotropin secretion, leading to decreased testosterone levels and testicular damage[19].

Aguilar-Mahecha et al. treated adult male rats with cyclophosphamide (70 mg/kg, i.p.) and compared them to a control group (saline solution, i.p.). Sixteen hours after injection, CP specifically disrupted the expression of stress response genes in germ cells during spermatogenesis[20]. Tımar et al. studied the effects of cyclophosphamide (CP) and saponin (SP) in 40 male mice divided into four groups. CP (15 mg/kg/week, i.p.) caused significant reductions in sperm viability, count, and normal morphology, alongside increased DNA fragmentation and malondialdehyde (MDA) levels. SP administration (2.5 mg/kg/day, i.p.) mitigated these effects, improving sperm parameters and enhancing antioxidant capacity[21]. Sabik et al. investigated the protective effects of vitamin E and ginger against cyclophosphamide (CP)-induced gonadal toxicity in 44 male rats. CP was administered at 20 mg/kg body weight for 14 days. Both the vitamin E + CP and ginger + CP groups had significantly higher testis weights compared to the CP group. The CP group showed the highest malondialdehyde (MDA) levels and the lowest testosterone levels. Testosterone levels were significantly higher in the vitamin E + CP and ginger + CP groups. Histopathological analysis revealed reduced spermatogonial cell death and apoptosis in these groups, demonstrating the protective effects of vitamin E and ginger[8].

Exposure to CP during chemotherapy, both before and after puberty, leads to abnormal sperm parameters. Higher CP doses are associated with an increased risk of infertility. In a study of 17 males, azoospermia was found in 58.8%, oligospermia in 29.4%, and normal sperm count in 11.8%[22]. High doses of CP can lead to azoospermia and hormonal disturbances. In a study of 31 male patients with Behçet's disease, CP treatment was found to increase the risk of infertility. These findings highlight the significant damage CP can cause to the male reproductive system[23]. Similar findings have been reported in studies involving other populations. These studies collectively emphasize the significant damage CP can cause to the male reproductive system[24,25]. Rocha et al. reported a 60% reduction in edema and inflammation in rats treated with 25 mg/kg RA[26]. Roland et al. demonstrated that RA provided protection against skin cancer[27]. Boonyarikpunchai et al. showed that RA, when administered at doses of 100 and 150 mg/kg, prevented both chronic and acute inflammation[28]. Our study aimed to explore the protective effects of RA against CP-induced testicular toxicity. CP is a commonly used alkylating agent known for its cancer-fighting and immune-suppressing properties. It is frequently used to treat various cancers, including lymphoma, breast cancer, ovarian cancer, and myeloblastoma, and to suppress the immune system in conditions such as rheumatoid arthritis and myasthenia gravis. Despite its therapeutic effectiveness, CP has been associated with several toxic effects, particularly on rapidly dividing cells, such as those in the gonads. These effects include nausea, vomiting, hair loss, and more serious reproductive issues, such as gonadal damage, which can ultimately lead to infertility. In light of this, our study aimed to determine whether RA, a compound known for its diverse biological activities, could mitigate the toxic effects of CP on the testes. To assess the protective potential of RA, we evaluated several parameters. To begin with, body weight changes were evaluated in the RA+CP group in comparison to the CP-only group. No significant difference in body weight was observed between pre- and post-experiment measurements within the RA+CP group ($p>0.05$), suggesting that RA may have prevented significant weight loss commonly associated with CP treatment (**Fig. 1**). Furthermore, to investigate the impact of RA on CP-induced oxidative damage, we measured malondialdehyde (MDA) levels, a biomarker of oxidative stress. The MDA levels were significantly lower in the RA+CP group (1.7±0.03 nmol/ml) compared to the CP group (2.5±0.9 nmol/ml), with a statistically significant difference ($p<0.05$) (**Fig. 2**). This reduction in MDA levels suggests that RA possesses antioxidative properties, potentially contributing to its protective role against CP-induced oxidative stress. Additionally, immunohistochemical analysis was performed to examine Bax expression, a pro-apoptotic marker, in the testes. In the RA+CP group, Bax expression was found to be absent in both seminiferous tubules and intertubular connective tissue (**Fig. 4**). This result indicates that RA treatment effectively inhibited Bax expression, suggesting a protective effect against CP-induced apoptosis. Finally, Western blot analysis was conducted to quantify Bax protein levels and further investigate the impact of RA on Bax expression. The results demonstrated a significant downregulation of Bax expression in the RA+CP group compared to the CP-only group (**Fig. 5**). This downregulation of Bax protein supports the hypothesis that RA attenuates CP-induced apoptosis in testicular tissues.

Our study demonstrates that rosmarinic acid (RA) provides significant protection against cyclophosphamide (CP)-induced gonadal toxicity in rats by modulating key apoptotic pathways. CP treatment led to a substantial increase in Bax protein expression, indicating an enhanced apoptotic response in testicular tissues. Bax, a pro-apoptotic protein, facilitates the release of cytochrome c from mitochondria, thereby initiating the intrinsic apoptotic pathway[29]. This upregulation of Bax is consistent with CP's well-established role in inducing oxidative stress and DNA damage, both of which activate apoptotic signaling cascades[30]. In contrast, RA treatment effectively counteracted the CP-induced upregulation of Bax, suggesting that RA protects against apoptosis by inhibiting Bax expression. This protective effect is likely due to RA's well-documented antioxidant and anti-inflammatory properties[31]. Further supporting this hypothesis, our bioinformatic analysis revealed that RA regulates several critical pathways related to the suppression of oxidative stress and endoplasmic reticulum (ER) stress—both of which are key contributors to Bax activation and apoptosis. Specifically, RA modulated pathways associated with cytochrome c release from mitochondria and ER stress, both of which are crucial players in apoptotic signaling. On the other hand, CP-induced toxicity was associated with the upregulation of oxidative stress and lipid peroxidation pathways, such as "cytochrome P450" and "response to oxidative stress." These findings align with the known role of CP in generating reactive oxygen species (ROS) through its metabolism, which leads to oxidative damage in gonadal tissues[32]. The observed increase in Bax expression is likely a direct consequence of CP-induced ROS production, as oxidative stress is a well-known trigger for the mitochondrial apoptotic pathway. Taken together, our findings suggest that RA mitigates CP-induced gonadal toxicity by modulating Bax expression and regulating key apoptotic pathways. By alleviating oxidative stress and maintaining mitochondrial integrity, RA emerges as a promising therapeutic strategy for protecting against chemotherapy-induced gonadal damage.

5. Conclusion

RA effectively mitigates CP- induced gonadal toxicity by modulating key apoptotic pathways, particularly through the inhibition of Bax protein expression and the reduction of oxidative stress. RA's antioxidant and anti-inflammatory properties contribute to preventing apoptosis in testicular tissues. These findings position RA as

a potential therapeutic agent for protecting against chemotherapy-induced gonadal damage.

Statement of ethics

Ethical approval was obtained from the Dicle University Animal Experiments Local Ethics Committee (ethical approval number: 2020/16).

Source of Finance

This study was supported Research Projects (DUBAP) with the by Dicle University Scientific project number TIP.21.003

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Minimally Invasive Approach for the Parotid Gland Neoplasms: A Multicenter Retrospective Analysis

Çağlar Eker[1], Özgür Sürmelioğlu[1], Muhammed Dağkıran[1], Özgür Tarkan[1], Süleyman Özdemir[1], Yusuf Kızıl[2], Utku Aydil[2]

1 Cukurova University, School of Medicine, Department of Otorhinolaryngology and Head & Neck Surgery, Adana, Türkiye
2 Gazi University, School of Medicine, Department of Otorhinolaryngology and Head & Neck Surgery, Ankara, Türkiye

Abstract

Aim: Recently extracapsular dissection (ECD) for the parotid gland neoplasm have gained popularity, but the data about functional outcomes and complication rates are still limited and surgical technique is not standard. In this multicenter study, we have evaluated the safety, complications, utility and functional outcomes of ECD and necessity of drain requirement.

Methods: This study was conducted as a retrospective multicenter study and two tertiary academic referral centers were involved. Records of the subjects who underwent extracapsular dissection between January 2015 and January 2017 were reviewed. Demographic data, size and location of tumors, results of fine needle aspiration cytology, intraoperative adverse events such as capsule rupture or facial nerve damage, postoperative complications, results of definitive pathology, and hospitalization time of the subjects were reviewed.

Results: A total of 37 subjects were included in the study. There were no subjects with permanent or transient facial nerve dysfunction in either group. No patient complained of symptoms of Frey syndrome. Seroma developed in two of 37 patients. No recurrence has been encountered during the follow up period (min: 36 and max: 72 months).

Conclusions: ECD is a safe technique with very low complications rates according to our results. Even without facial nerve monitoring, ECD could be performed without any damage to the nerve, if surgeon is experienced. Preoperative evaluation is important and patients with small, mobile and solitary benign parotid lesions are good candidates for ECD.

Keywords: *Neoplasm; parotid surgery; minimally invasive surgery; extracapsular dissection*

1. Introduction

The majority of salivary gland neoplasms originate from the parotid gland, and neoplasms of the parotid gland account for 3% of all head and neck neoplasms[1-3]. Pleomorphic adenomas, also known as benign mixed tumors, are the predominant histologic subtype, accounting for 85% of all salivary gland neoplasms[2]. The great majority (85%) of parotid gland neoplasms arise from the superficial lobe[3].

Surgical techniques are the primary method for treating salivary gland tumors. The range of surgical options for parotid gland tumors includes enucleation, partial superficial parotidectomy (PSP), superficial parotidectomy (SP), total parotidectomy, or radical parotidectomy[4-6]. The choice of surgical approach is determined by factors such as the size of the tumor, histological results, the extent of the tumor, the stage (if it is malignant), and the location of the tumor (e.g., whether it is in the superficial or deep lobe, or in the parotid tail).

The treatment objectives include the complete and en bloc excision of the lesion with clearly defined margins, the preservation of facial nerve functionality, and the maintenance of the natural facial appearance, especially in the case of benign lesions. Since traditional enucleation results in increased recurrence rates, SP was regarded as the acceptable least comprehensive surgery for treatment of parotid gland tumors for decades.

Enucleation is not commonly used as a surgical approach for treating these tumors due to the elevated risks of capsule rupture and inadequate therapy, which are associated with a high likelihood of tumor recurrence. The risks of tumor recurrence range from 20% to 45%[2,7]. Nevertheless, the utilization of the conventional parotidectomy procedure significantly decreases recurrence rates. The conventional procedure for parotidectomy involves a comprehensive dissection that begins with the identification of the facial nerve, followed by the removal of the tumor together with either the

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superficial or deep lobe of the parotid gland[8,9]. The risk of facial nerve injury is significantly higher in this surgical treatment[10]. In order to mitigate these hazards, certain surgical methods have been implemented, such as PSP or extracapsular dissection (ECD)[11,12]. ECD needs fewer incisions and attempt to protect the parotid parenchyma and minimize the need for facial nerve dissection, thus reducing the risk of facial nerve paralysis, injuries, and other problems[13,14]. The use of limited surgery leads to improved cosmetic outcomes.

Currently, there is a growing interest in ECD procedures. However, there is a lack of comprehensive data regarding the functional outcomes and rates of complications. Additionally, there is no universally accepted standard surgical approach for ECD. This multicenter study aims to assess the safety, complications, efficacy, and functional outcomes of ECD and determine the necessity of drain requirement.

2. Materials and Methods

This investigation was carried out as a retrospective multicenter study, involving two tertiary academic referral centers. The study received approval from the local ethics committee (No: 2015/043). The records of individuals who had ECD from January 2015 to January 2017 were examined. The surgical procedures were conducted by two proficient surgeons, specifically the first and last authors. Prior to surgical operations, all participants had evaluation using ultrasonography or magnetic resonance imaging, as well as fine needle aspiration cytology (FNAC). Participants with malignant neoplasms, suspected malignancy, deep lobe tumors, and revision procedures were not included in the study. The study examined many factors including demographic information, tumor characteristics such as size and location, results of FNAC, any challenges encountered during surgery such as capsule rupture or facial nerve injury, postoperative complications, results of definitive pathology, and length of hospital stay for the individuals.

Subjects in group I were operated on by the first author, while subjects in group II were operated on by the last author.

2.1. Surgical Technique

All of the procedures were performed general anesthesia. Nerve monitoring was used in group I and not used in group II. In group I, parotidectomy incision, Lazy S, was used but in subjects whose masses are located in parotid tail, a modified smaller incision was used. Skin incision of the pre-auricular region was avoided in these subjects. Quite small incisions were made in all subjects according to tumor location in group II. The skin flap is elevated in a plane immediately over the parotid fascia to expose the periphery of the tumor by a minimum of 1 cm in both groups shown in **Figure 1**. After the skin flap has been raised, the mobility and margins of the tumor is controlled, attention was paid to maintain the integrity of the tumor capsule by performing a wide dissection of the parenchyma surrounding the mass without identification of the facial nerve or branches nerve shown in **Figure 2**. Approximately two to three millimeters normal tissue cuff left around mass. Blunt dissection was performed parallel to the nerve. If a facial nerve branch was concurred, the branch was closely tracing during the dissection. If the lesion had intraoperative features such as infiltration into surrounding structures, a frozen section was performed. In case of malignancy in the frozen section pathology report, classical superficial parotidectomy or total parotidectomy was performed to obtain clean oncological margins. Latex penrose drains were used in group I and were not used in group II.

2.2. Statistical Analysis

T-test or Mann Whitney U test were used for continuous variables and Chi-square test was used for categorical variables between independent groups. Data expressed as means±SDs for continuous variables and as number (n) and percent (%) for categorical variables. The analyses were performed using the statistical package SPSS v22.0.

Figure 1

Small skin incision and minimally skin flap elevation

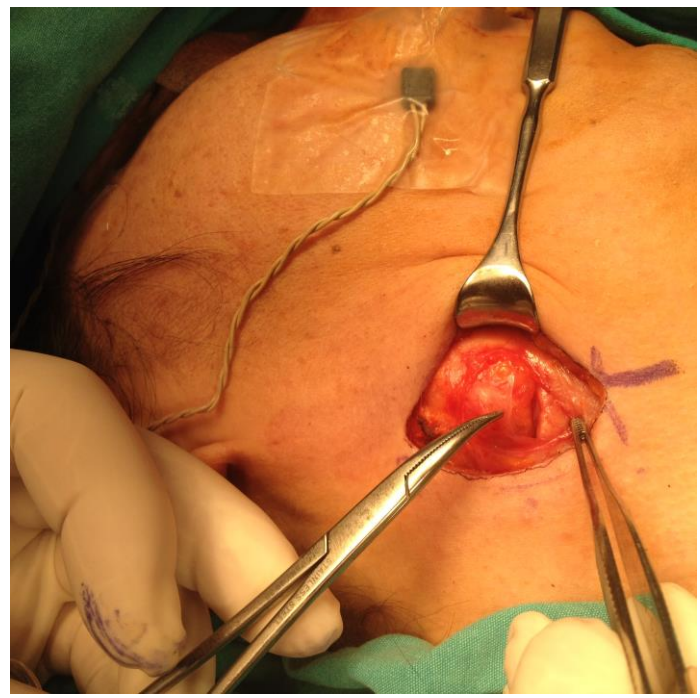
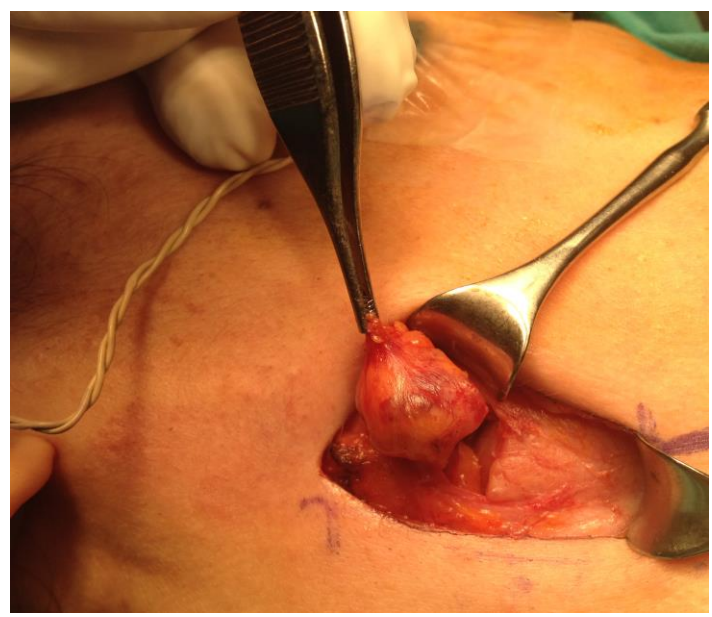


Figure 2

Performing a wide dissection of the parenchyma surrounding the mass without identification of the facial nerve and its branches



3. Results

A total of 37 (26 female, 11 male) subjects were included in the study. There were 17 patients (8 male/9 female) in group I and 20 patients (3 male/17 female) in group II. The mean ages were 45.5 (SD 13.8 years) and 53.3 (SD 13.1 years) in groups I and II, respectively. Demographic characteristics of the study population are described in **Table 1**. Results of preoperative FNAC of all subjects were either benign or non-diagnostic (**Table 2**). In all subjects, the early postoperative period was uneventful without any local complication (edema and/or surgical site bleeding, facial paralysis) or systemic complications (fever, etc.). There were no subjects with permanent or transient facial nerve dysfunction in either group. No patient complained of symptoms of Frey syndrome. Seroma developed in two of 37 patients (One patients in group I and another in group II) and there was not any statistical different between group I and II (p>0,9). Seroma was recovered after aspiration and pressure dressing in two days in both subjects. Mean largest tumor diameter was found 2,1-/+0,7 in group I and 1,8-/+0,2 in group II. No recurrence has been encountered during the follow up period (min: 36 and max: 72 months).

Table 1

Demographic features of patients.

		Group I	Group II	Total
Gender	M	8	3	11
	F	9	17	26
Age (Min-Max)		45.5(19-64)	53.3(18-73)	49.4(18-73)
Tumor localization	R	11	11	22
	L	6	9	15

Table 2

Preoperative FNAC results

FNAC Results	Group I (%)	Group II (%)	Total (%)
Benign lesion	3(17)	1(5)	4(10.8)
Atypic cells	5(29.4)	0	5(13.5)
Pleomorphic adenoma	7(41.2)	4(20)	11(29.7)
Basaloid neoplasm	1(5.9)	4(20)	5(13.5)
Lymphoid cells	1(5.9)	3(15)	4(10.8)
Warthin tumor	0	5(25)	5(13.5)
Mesenchymal tumor	0	1(5)	1(2.7)
Chronic sialadenitis	0	1(5)	1(2.7)
Lipomatosis	0	1(5)	1(2.7)

FNAC: Fine needle aspiration cytology

4. Discussion

Ensuring a wide tumor free margin, even if benign tumors, has paramount importance to prevent recurrences in benign neoplasms of the parotid gland. In case of recurrence, there is a risk of malignant transformation, especially in pleomorphic adenoma. Aside from achieving tumor-free margins, the identification of the facial nerve and its branches is also a crucial concern. Superficial parotidectomy, facial nerve branches are dissected and entire superficial lobe is resected has been the standard of surgery for a long time. Although the rates of tumor recurrence have reduced with SP, there are significant risks associated with completely dissecting the facial nerve. Additionally, removing normal parotid tissue might result in cosmetic abnormalities and other problems, such as salivary fistula or Frey syndrome[14,15].

Conservative surgical techniques have been increasingly popular for treating benign parotid neoplasms. This is because they help reduce complications and enhance functional results, in besides achieving good oncological outcomes. The most often employed conservative procedures for parotid surgery are PSP and ECD[4,13,15]. ECD is distinct from conservative parotid procedures. During this procedure, the facial nerve is not identified and the parotid mass is meticulously dissected and excised with surgical margins of 2-3 mm[12,14].

Recent studies indicate that the extracapsular dissection approach can reduce problems without increasing the recurrence rate[13-15]. In a study, the authors found that there was no significant disparity in recurrence rates (2%) between ECD and SP[15]. This analysis included 503 patients who underwent ECD and 159 patients who underwent SP. A comparative study was conducted to assess the surgical results and cost-effectiveness of ECD vs SP[16]. This study covered a total of 46 surgeries, which consisted of both ECD and SP procedures. According to their report, ECD is a successful, cost-effective, and safe technique for treating benign parotid lesions. A study provided highly promising initial findings about the efficacy of ECD as the exclusive treatment for specifically chosen patients with small-sized malignant tumors that are low-stage, low-grade, and placed inferiorly[17].

Our study has found that ECD is a safe approach, even without facial nerve monitoring, when performed by an experienced surgeon. We did not detect any early local surgical complications such as edema, surgical site hemorrhage, or facial paralysis, nor did we observe any systemic symptoms like fever. No nerve dysfunction or Frey syndrome was observed in any group. Another surgical option for benign parotid neoplasms is PSP. A recent systematic review and meta-analysis has been conducted to compare the effectiveness of ECD and PSP for treating benign lesions of the parotid glands[18]. The analyzed outcomes pertain to the complications. This meta-analysis comprised seven trials, encompassing a total of 1641 patients. The incidence of temporary facial nerve damage and Frey syndrome was lower in the ECD group. There was no significant difference between the two groups in terms of the rates of persistent facial nerve injury, recurrence, infection, and salivary fistula/sialocele. Based on this study, it was seen that ECD had a lower likelihood of problems. However, the current findings do not provide enough evidence to definitively state that ECD is more successful than PSP.

Our study demonstrates that meticulous dissection and surgical expertise are crucial factors for achieving a successful ECD. Facial nerve monitoring is beneficial for avoiding legal concerns, although doing ECD without nerve monitoring can still be done without causing injury to the facial nerve. Another distinction between the two doctors and hospitals was the utilization of drains. Based on our findings, if a meticulous dissection is conducted with a small incision in specific individuals, the use of a drain would be unnecessary. Postoperative scar and quality of life may be improved by closure without drainage.

One primary constraint of our investigation is the limited size of the study population. Despite the small study population, our findings about the preservation of facial nerve function and the absence of complications after ECD without nerve monitoring and drainage usage are significant contributions to the improvement of the ECD technique. Another constraint would be the presence of selection bias among the subjects. Nevertheless, it is important to note that ECD should only be conducted on a certain subset of individuals with parotid tumors, and we strongly recommend meticulous pa-

tient selection to maximize outcomes.

5. Conclusion

To summarize, our results indicate that ECD is a safe method with minimal rates of problems. Even in the absence of facial nerve monitoring, a competent surgeon can conduct ECD without causing any harm to the nerve. If a precise and careful dissection can be performed using a small incision, drainage is not required. Preoperative assessment is crucial, and individuals with small, mobile, and solitary benign parotid lesions are suitable candidates for ECD.

Statement of ethics

Ethical approval was obtained from the Cukurova University Ethics Committee (ethical approval number: 2021/116).

Conflict of interest statement

The authors declare that they have no conflict of interest.

Author Contributions

Concept – CE, MD, OT, UA; Design - CE, OS, OT, SO; Supervision - OS, YK, UA; Resources – CE, MD, SO, YK; Data Collection and/or Processing – CE, OS, UA; Analysis and/or Interpretation – CE, OT, YK, UA; Literature Search – CE, OS, SO; Writing Manuscript – CE, OS, MD, OT, SO, YK, UA; Critical Review – CE, OS, MD, OT, SO, YK, UA.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Predictive Factors Increasing the Risk of Malignancy in Thyroid Follicular Neoplasia

Fatma Özarslan[1], *Hüseyin Özgür Aytaç*[1], *İlker Murat Arer*[2], *Eda Meler Ertorer*[3], *Nazım Emrah Kocer*[4], *Murathan Erkent*[5], *Hakan Yabanoğlu*[1]

1 Başkent University Adana Dr. Turgut Noyan Application and Research Center, Department of General Surgery, Adana, Türkiye
2 Üsküdar University School of Medicine, Department of General Surgery, İstanbul, Türkiye
3 Başkent University Adana Dr. Turgut Noyan Application and Research Center, Department of Endocrinology, Adana, Türkiye
4 Başkent University Adana Dr. Turgut Noyan Application and Research Center, Department of Pathology, Adana, Türkiye
5 Başkent University School of Medicine, Department of General Surgery, Ankara, Türkiye

Abstract

Aim: 22-42% of patients with thyroid nodules are diagnosed as Bethesda category IV "Follicular Neoplasia (FN)". Although hemithyroidectomy (HT) is the recommended treatment for follicular neoplasia, some characteristics of the patient or the disease make total thyroidectomy (TT) the treatment of choice. The aim of this study is to evaluate our clinical results in patients with FN who underwent surgery and determine predictive risk factors in patients with malignant pathology results.

Methods: 364 patients were included in the study. Fine needle aspiration biopsy (FNAB) with a FN result was defined as a "target nodule". Demographic, radiological and clinical characteristics of the two groups were determined. Two different types of surgical procedures were applied to the patients: HT or TT.

Results: The number of patients was 199 (54.7%) in Group 1 and 165 (45.3%) in Group 2. Malignancy was incidentally detected in 138 patients (37.9%) outside the target nodule. The risk of malignancy was higher in those under 45 compared to those aged 45 and older. Malignancy was observed in 123 (42.7%) of female patients and 42 (55.3%) of male patients. Additionally, the risk of malignancy increased in patients with nodules measuring 2 cm or larger.

Conclusions: In FN cases, the risk of malignancy increases in males, in nodules 2 cm and above, and in younger age groups. According to our data, the risk of malignancy in FN is 45.3%. Additionally, the rate of incidental thyroid cancer is 37.9%. We attribute the higher rates of these findings compared to literature to the increased frequency of thyroid cancer in our region.

Keywords: *Follicular Neoplasia; nodule size; thyroid nodules*

1. Introduction

Thyroid diseases are common in our country, as they are worldwide. Ultrasound (US) detects nodules in 10-67% of the adult population, and in autopsy series, nodules are found in more than 50% of thyroid glands. The detection of malignancy in 9.2% to 14.8% of these nodules during cytological diagnosis emphasizes the importance of distinguishing between malignant and benign nodules [1]. However, since cytological examination may not always yield sufficient results, uncertainties can arise in the management of thyroid nodules. Thyroid nodules must be defined radiologically, clinically and most importantly cytologically for treatment planning. The average sensitivity of fine needle aspiration biopsy (FNAB) for detecting thyroid cancers has been found to be 83%, specificity 92%, and diagnostic accuracy 95% [2,3]. Bethesda System for Reporting Thyroid Cytopathology was introduced by the National Cancer Institute in 2009 in order to standardize the results of cytological sampling obtained through FNAB [4]. This reporting system, most recently updated in 2023 [5], still defines "Follicular Neoplasm (FN)" in category IV as a gray area (**Figure-1**). Problems encountered during the diagnostic process of patients in this category continue to pose significant challenges in treatment planning. Between 22-42% of patients undergoing FNAB receive a Bethesda category IV "Follicular Neoplasm" diagnosis [6]. The malignancy rate for Bethesda category IV ranges from 10-40% [4]. This category is among the most controversial groups within the system because it is not possible to differentiate between benign and malignant diseases cytologically in FN diagnosis. Cytological examination with FNAB is significantly successful in distinguishing between papillary thyroid carcinoma (PTC) and benign diseases. However, it is difficult to differentiate between

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follicular thyroid carcinoma (FTC) (**Figure-3**), follicular variant papillary thyroid carcinoma (fvPTC) (**Figure-4**), benign follicular adenoma (**Figure-2**), and diseases such as hyperplastic nodular goiter in cases of follicular lesions classified as FN [7-9].

Currently, while the recommended treatment method for patients diagnosed with FN is hemithyroidectomy (HT), the characteristics of the patient and the disease affect treatment management, and total thyroidectomy (TT) may be applied in selected cases. Reasons for performing TT include multinodular goiter, discrepancies between FNAB results and radiological and clinical findings, a family history that increases the risk of thyroid cancer, exposure to radiation in the head and neck area, the patient's preference to avoid a second surgical procedure in cases requiring completion thyroidectomy, and particularly in our country, the common occurrence of hypothyroidism (due to thyroiditis) in women, leading to them receiving levothyroxine treatment. There are ongoing discussions in the literature regarding the treatment methods applied in most series. The aim of this study is to evaluate the clinical outcomes in patients diagnosed with FN as a result of FNAB and undergoing surgery, as well as to investigate the impact of predictive factors we determine on the choice of surgical type concerning malignancy.

Figure 1

Follicular Neoplasia: Microfollicles composed of thyrocytes exhibiting nuclear atypia on a colloid-poor background *(MGG X100).*

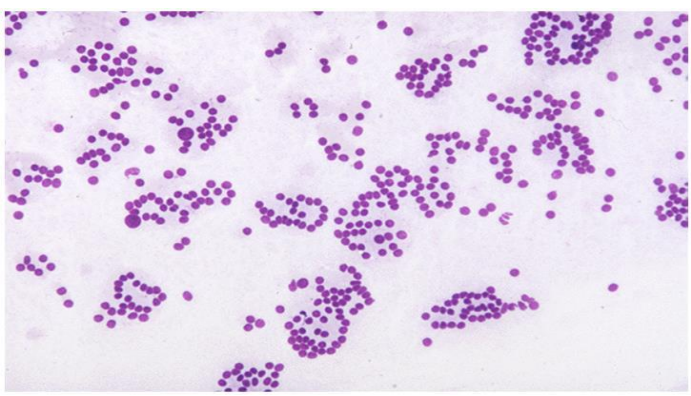


Figure 2

Follicular Adenoma: A lesion characterized by small follicles that are generally poor in colloid, surrounded by a thick fibrous capsule, exhibiting signs of pressure against the surrounding thyroid tissue *(HE X40).*

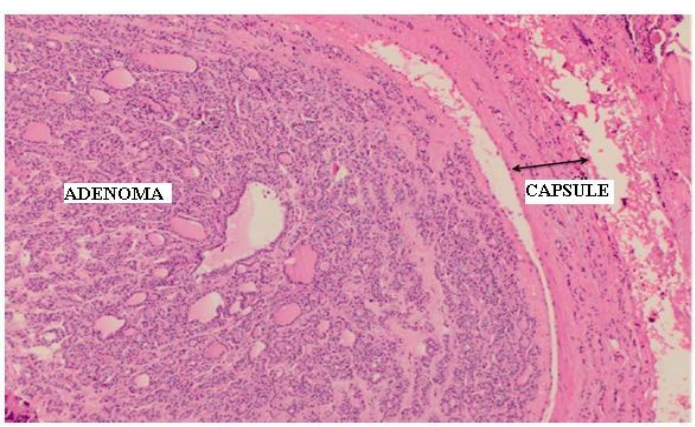


Figure 3

Follicular Carcinoma: A minimally invasive carcinoma characterized by microfollicular structures that exhibit complete capsule invasion and are poor in colloid *(HE X100).*

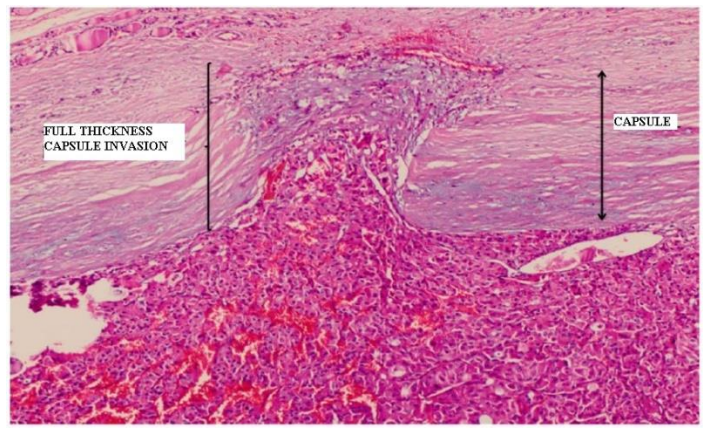
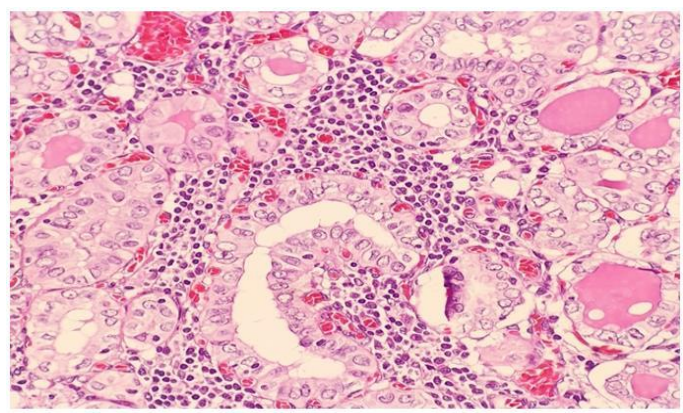


Figure 4

Follicular Variant Papillary Carcinoma: Follicular structures composed of thyroid cells exhibiting features of papillary carcinoma, characterized by nuclear enlargement, clearing, irregular nuclear membranes, peripheral placement of small single nucleoli, grooves, and intranuclear pseudoinclusions. The lesion is encapsulated and presents an infiltrative pattern, with no true papillary architecture observed *(HE X400).*



2. Materials and Methods

The data for our study were retrospectively obtained from the files of 364 patients who underwent surgery due to a diagnosis of follicular neoplasia (FN) at Başkent University School of Medicine Adana Dr. Turgut Noyan Application and Research Center between January 2016 and July 2021. Our study received approval from the Ethics Committee of Başkent University School of Medicine with the number KA 22/125. Patients who presented during the specified period and were found to have thyroid nodules through physical examination, laboratory, and radiological investigations, and for whom fine-needle aspiration biopsy (FNAB) was indicated, were included in the study. During this process, data were collected from patients with FN detected by FNAB who subsequently underwent surgical intervention. Data collected included age, gender, medical history (family history, radiation exposure to the head and neck,

etc.), medications, comorbidities, previous thyroid surgeries, known thyroid diseases, presenting complaints, physical examination findings, ultrasound characteristics (echogenicity, calcification, vascularity, internal nodule structure, nodule borders, vertical and horizontal size ratios, halo, nodule size), pathology results (type of cancer in the target nodule), incidental cancer rates and types and rates of complementary thyroidectomy. Predictive risk factors for malignancy in follicular neoplasia were determined through a literature review. Nodules with FN diagnosed via FNAB were defined as the "target nodule." Patients were divided into two groups based on whether the target nodule was malignant or benign. Those with benign target nodules were classified as Group 1, while those with malignant target nodules were classified as Group 2. A comparative analysis was conducted between the two groups regarding demographic, radiological and clinical parameters. Additionally, both Group 1 and Group 2 were further subdivided into three subgroups based on nodule size. Nodules measuring 2 cm or less were classified as A (1A, 2A), those between 2-4 cm as B (1B, 2B), and those 4 cm or larger as C (1C, 2C). The malignancy risk based on nodule size was compared both between the two groups and within their respective subgroups. The types and subtypes of thyroid cancers in patients with malignant target nodules and incidental malignancies (nodules outside the target) were identified. Patients underwent either hemithyroidectomy (HT) or total thyroidectomy (TT). Those who underwent HT and were classified as high-risk for malignancy based on pathology results underwent complementary thyroidectomy.

2.1 Statistical Method

Statistical analyses were performed using SPSS version 25.0. The normal distribution of variables was assessed using the Shapiro-Wilk test. Descriptive analyses presented mean ± standard deviation and median (min-max) values. The Mann-Whitney U test was used for evaluating non-normally distributed variables between the two groups. Categorical variables were expressed in terms of frequency and percentage. The relationships between categorical variables were examined using the Chi-Square Test. Differences between groups were determined using Dunn's Bonferroni Test. Univariate logistic regression analysis was conducted to identify factors influencing the risk of malignancy. Independent variables with p-values of 0.25 or below were included in the model. A p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 364 patients were included in the study. Group 1 consisted of 199 patients (54.7%), while Group 2 included 165 patients (45.3%). Of the patients, 288 (79.12%) were female and 76 (20.88%) were male. The average age was 46.77 ± 13.43 years, ranging from 14 to 81 years. There were 160 patients (43.96%) under 45 years old and 204 patients (56.04%) aged 45 and older. In Group 1, 62.30% of the patients were 45 years and older, while in Group 2, 37.70% were in the same age group. Univariate logistic regression analysis to determine factors influencing the risk of malignancy showed that age (under 45 and 45 and older) significantly affects the risk of malignancy. The risk of malignancy was higher for those under 45 years compared to those 45 and older ($p > 0.001$). Variables with a significance level of $p \leq 0.25$ would be included in the multivariate logistic regression model; however, only one independent variable, age, met this criterion. Among female patients, 123 (42.7%) were diagnosed with malignancy, while 42 male patients (55.3%) were diagnosed as well.

Table 1

Demographic data of the patients

		Benign (n=199) (Group 1)		Malignant (n=165) (Group 2)		p
		n	%	n	%	
Complaint	Neck swelling	22	(11.06)	28	(16.97)	0.248
	Incidental	23	(11.56)	24	(14.55)	
	Goiter follow-up	43	(21.61)	40	(24.24)	
	Hypothyroidism	5	(2.51)	4	(2.42)	
	Hyperthyroidism	7	(3.52)	2	(1.21)	
	Compression sign	10	(5.03)	10	(6.06)	
	Extrathyroidal endocrine disease	29	(14.57)	16	(9.70)	
	Nodule detected on PET/BT scan	3	(1.51)	5	(3.03)	
	Signs of thyroiditis	1	(.50)	3	(1.82)	
	Pain in neck	9	(4.52)	2	(1.21)	
Concomitant thyroid disease	Hyperthyroidism	37	(18.59)	23	(13.94)	0.623
	Hypothyroidism	12	(6.03)	12	(7.27)	
	Thyroid nodule	57	(28.64)	47	(28.48)	
	Thyroid cancer operation	1	(0.50)	0	(0.00)	
	Thyroidectomy (Benign pathology)	6	(3.02)	2	(1.21)	
Family history of thyroid cancer	Yes	8	(4.02)	9	(5.45)	0.518
	No	191	(95.98)	156	(94.55)	
Levothyroxin use	Yes	19	(9,55)	14	(8,48)	0.725
	No	180	(90,45)	151	(91,52)	
Sex	Female	165	(82,91)	123	(74,55)	0.051
	Male	34	(17,09)	42	(25,45)	

Although the malignancy rate was higher in male patients, there was no statistically significant difference between genders regarding malignancy rates (p = 0.051). The average age of patients in Group 2 was 44.26 ± 14.02 years, while the average age in Group 1 was 48.81 ± 12.59 years. There was a statistically significant difference in the ages of patients between both groups, with Group 1 having a higher average age (p = 0.001).

Reasons for hospital admission included palpable neck swelling in 50 patients (13.74%), incidental detection of thyroid nodules in 47 patients (12.91%), known follow-up of multinodular goiter in 83 patients (22.80%), follow-up due to hypothyroidism in 9 patients (2.47%), follow-up due to hyperthyroidism in 9 patients (2.47%), compressive symptoms in 20 patients (5.49%), diagnosis at another center in 64 patients (17.58%), follow-up due to non-thyroidal endocrine disorders in 45 patients (12.36%) and thyroid nodules detected on PET/CT in 8 patients (2.20%). One patient (0.27%) was under follow-up due to recurrence after thyroidectomy (malignancy). Thirteen patients (3.57%) were under follow-up due to benign thyroidectomy, 4 patients (1.10%) presented with thyroiditis symptoms, and 11 patients (3.02%) presented with complaints of pain in the neck and throat.

Both Group 1 (21.61%) and Group 2 (24.24%) had the most common reason for admission as the detection of FN from biopsies performed on patients under follow-up for multinodular goiter. When comparing presenting complaints between the two groups, no statistically significant difference was found (p > 0.05). In terms of medical history, 60 patients (16.48%) had hyperthyroidism (37 in Group 1 and 23 in Group 2), and 33 patients (9%) had hypothyroidism (19 in Group 1 and 14 in Group 2). There was no statistically significant difference regarding functional disorders between the groups (p > 0.05). A family history of thyroid cancer was present in 17 patients (4.67%) (8 in Group 1 and 9 in Group 2), and one patient had previously been operated on for papillary thyroid cancer. No statistically significant difference was observed between the groups regarding family history (p > 0.05) (**Table-1**).

Preoperative ultrasound (USG) examination evaluated features for malignancy in nodules: microcalcifications were present in 31.32%, solid components in 99.45%, irregular borders in 6.89%, absence of halo in 66.21%, hypoechogenicity in 75.6%, anteroposterior to transverse diameter ratio greater than 1 in 40.3%, and vascularity in 51.3% of patients. When comparing all USG parameters between Groups 1 and 2, no statistically significant differences were found (**Table-2**).

63.32% of patients in Group 1 and 55.76% in Group 2 were found to have bilateral thyroid nodules in the USG examination. In terms of cystic characteristics of nodules, significant differences were observed among benign groups and malignant groups with nodule sizes smaller than 20 mm, between 20 mm and 40 mm, and larger than 40 mm (p = 0.032). Among those with malignant nodules larger than 40 mm, 50% had cystic features, while 19.32% in the 20-40 mm group and 31.31% in the benign group had cystic features.
Cases in Group 2 were subdivided according to nodule size in order to evaluate the relationship between malignancy risk and size. Those with nodules measuring 2 cm or less were classified as 2A, those between 2-4 cm as 2B, and those 4 cm or larger as 2C. There were 89 patients in Group 2A, 66 in Group 2B, and 10 in Group 2C.

The average nodule size across all groups was 20.71 ± 10.08 mm. The average nodule size in Group 1 was 20.86 ± 9.31 mm, while in Group 2 it was 20.53 ± 10.97 mm.

When comparing nodule sizes between groups, no statistically significant difference was observed (p > 0.05). The average nodule size in Group 2A was found to be 12.66 ± 3.54 mm. The nodule size in Group 1 was larger than that in Group 2A, and the results were statistically significant (p < 0.001) (**Table-3**). There was no statistically significant difference in average age between Groups 1 and 2A. The average nodule size in Group 2B was 27.53 ± 5.87 mm, which was significantly larger compared to Group 1 (p < 0.001). The average age of patients in Group 2B was 43.49 ± 14.77 years, and they were significantly younger than those in Group 1 (p = 0.040) (**Table-3**). The average nodule size in Group 2C was found to be 47.90 ± 8.02 mm, which was also statistically significantly larger than that in Group 1 (p < 0.001) (**Table-3**).

Table 2

Malignancy risk of the nodule with follicular neoplasia cytology according to ultrasound findings

		Benign (n=199) (Group 1)		Malignant (n=165) (Group 2)		p
		n	%	n	%	
Echogenity	Hypoechoic	149	(75.25)	126	(76.36)	0.425
	Hyperechoic	4	(2.02)	1	(0.61)	
	Isoechoic	36	(18.18)	26	(15.76)	
	Heterogenous	9	(4.55)	12	(7.27)	
Microcalcification	Yes	60	(30.15)	54	(32.73)	0.598
	No	139	(69.85)	111	(67.27)	
Solid component	Yes	197	(99.49)	163	(99.39)	0.999
	No	1	(0.51)	1	(0.61)	
Cystic	Yes	62	(31.31)	47	(28.68)	0.584
	No	136	(68.69)	117	(71.34)	
Mixed	Yes	59	(29.80)	48	(29.27)	0.912
	No	139	(70.20)	116	(70.73)	
Border	Regular	181	(91.41)	157	(95.15)	0.161
	Irregular	17	(8.59)	8	(4.85)	
Vascularity	Decreased	96	(48.48)	80	(48.48)	0.999
	Increased	102	(51.52)	85	(51.52)	
Halo	Yes	68	(34.17)	55	(33.33)	0.866
	No	131	(65.83)	110	(66.67)	

Table 3

Comparison of nodule size and age in Group 1 and 2A, 2B, 3C

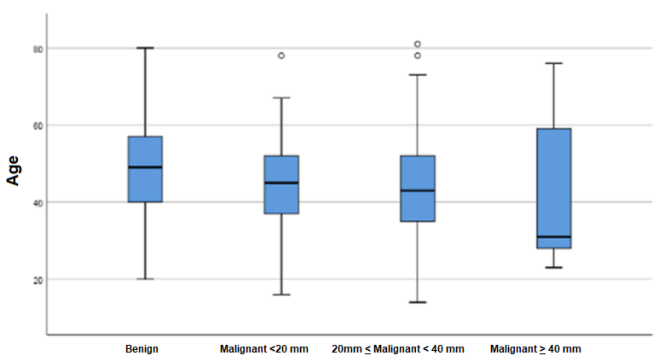
		Benign (Group 1)		Malignant <20 mm (Group 2A)		p
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2A	Age	48.81±12.59	49(20-80)	45.16±12.70	45(16-78)	0.202
	Nodule size	20.68±9.18	20(5-55)	12.66±3.54	12(6-19)	<0.001
		Benign (Group 1)		20 mm≤ Malignant <40 mm (Group 2B)		
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2B	Age	48.81±12.59	49(20-80)	43.49±17.77	43(14-81)	0.040
	Nodule size	20.68±9.18	20(5-55)	27.53±5.87	27(20-40)	<0.001
		Benign (Group 1)		Malignant ≥40 mm (Group 2C)		
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2C	Age	48.81±12.59	49(20-80)	41.69±19.10	31(23-76)	0.191
	Nodule size	20.68±9.18	20(5-55)	47.90±8.02	45(42-70)	<0.001

Table 4

Incidental thyroid cancer exccept target thyroid nodule

	Benign (Group 1)		Malignant <20 mm (Group 2A)		Malignant 20-40 mm (Group 2B)		Malignant >40 mm (Group 2C)	
	n	%	n	%	n	%	n	%
Micropapillary carcinoma	60	88.24	36	90.00	21	75.00	2	100.00
PTC/Follicular variant	6	8.82	3	7.5	4	14.29	-	-
PTC/Classical variant	-	-	1	2.50	1	3.57	-	-
PTC/Tall cell variant	1	1.47	-	-	1	3.57	-	-
PTC/Oncocytic variant	-	-	-	-	1	3.57	-	-
Hurthlecell carcinoma	1	1.47	-	-	-	-	-	-

** PTC: Papillary thyroid cancer.*

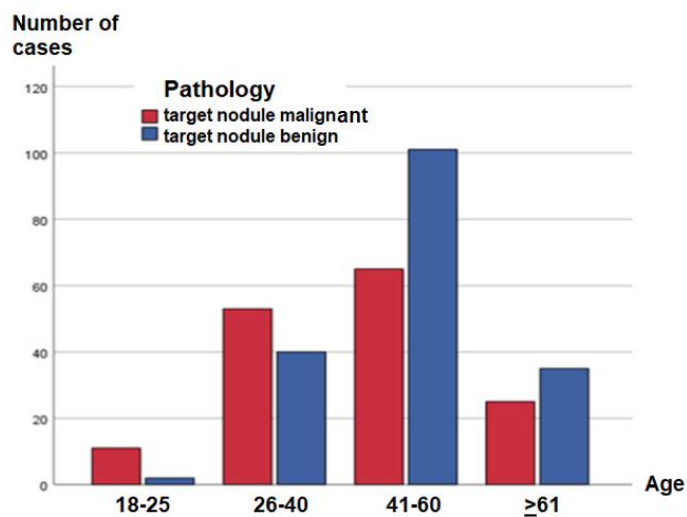


Graph 1

The relationship between nodule size and patient age and malignancy

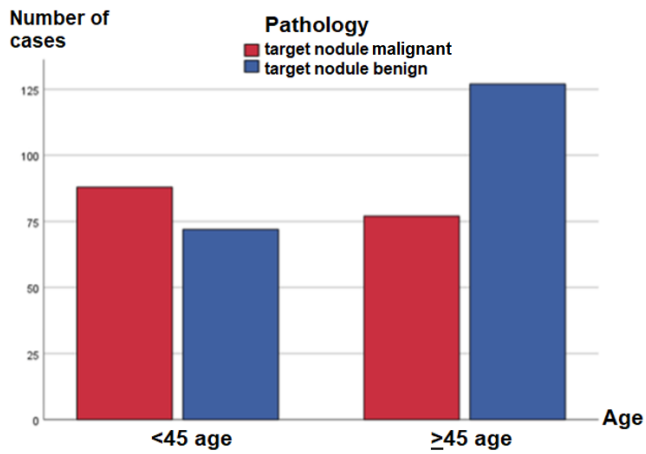
When benign (Group 1) and malignant cases in each of the three subgroups (Group 2A, 2B, 2C) were evaluated together according to age distribution, it was determined that the increase in nodule size and younger patient age increased the likelihood of malignancy ($p < 0.001$) (**Graph-1**).

Given that patient age could be another predictor of the malignancy potential of nodules diagnosed with FN, cases were evaluated in four age groups. Among 16 patients ages between 18-25 years, 11 (68.75%) had malignancies, while 5 (31.25%) had benign diagnoses. Among 108 patients ages between 25-40 years, 55 (50.93%) had malignancies and 53 (49.07%) had benign diagnoses. Among 168 patients ages between 41-60 years, 70 (41.67%) had malignancies and 98 (58.33%) had benign diagnoses. Among 72 patients over 61 years old, 29 (40.28%) had malignancies and 43 (59.72%) had benign diagnoses. The malignancy rate was found to be higher in younger age groups (**Graph-2**). In the 25-40 age group, the number of malignant pathologies exceeded that of benign, but this trend reversed in the 41-60 age group, suggesting that predictions regarding malignancy and age will differ between these two groups. A repeated chi-square analysis suggested that 160 cases were under 45 years of age, while 204 were 45 years and older.



Graph 2

Distribution of pathology results by age groups



Graph 3

Distribution of pathology results according to age 45

Among those under 45, 88 (55%) were diagnosed with malignancy, and 72 (45%) were diagnosed with benign pathology. Among those over 45 yaers, 77 (27.7%) were diagnosed with malignancy and 127 (62.3%) were diagnosed with benign pathology. The likelihood of FN cytology nodules being malignant was found to be statistically significantly higher in cases under 45 years ($p < 0.001$). In the group under 45 years of age, 88 (55%) cases were diagnosed with malignant pathology, and 72 (45%) cases were diagnosed with benign pathology. In the group over 45 years of age, 77 (27.7%) cases were diagnosed with malignant pathology, and 127 (62.3%) cases were diagnosed with benign pathology. The likelihood of malignancy in FN cytology cases was found to be statistically significantly higher in the group under 45 years of age ($p<0.001$) (**Graph-3**).

Upon examining the pathological evaluations of patients, the most frequently seen histological subtype in Group 2A, where the target nodule was malignant, was micro-papillary thyroid cancer (n = 44, 49.44%). The most commonly seen subtype in Group 2B was follicular variant papillary thyroid cancer (n = 34, 51.52%), and similarly, in Group 2C, the most frequently seen subtype was also follicular variant papillary thyroid cancer (n = 7, 70%). Among all malignant cases (165 patients), the most frequently observed histological subtypes were micro-papillary thyroid cancer in 48 (29%) patients and follicular variant papillary thyroid cancer in 57 (34.5%) patients. Follicular thyroid cancer was observed in 8 (4.8%) patients.

Incidental thyroid malignancies were observed in 138 patients (37.9%) outside of the target nodule. Among these, 119 had micro-papillary thyroid cancer, 13 had follicular variant papillary thyroid cancer, 2 had classic variant papillary thyroid cancer, 2 had tall cell variant papillary thyroid cancer, 1 had oncocytic variant papillary thyroid cancer, and 1 had Hurthle cell carcinoma. The rate of incidental thyroid cancer was observed to be 34.1% (68 out of 199 patients) in Group 1 and 42.4% (70 out of 165 patients) in Group 2. In both groups, the most frequently observed histological type was micro-papillary thyroid cancer (88.24% in Group 1 and 84.29% in Group 2) (**Table-4**). In Group 1, 130 patients and in Group 2, 118 patients underwent bilateral total thyroidectomy, while 69 patients in Group 1 and 47 patients in Group 2 underwent unilateral thyroidectomy. There was no statistically significant difference between the two groups regarding the surgical technique. In Group 2, 27 patients (16.36%) underwent complementary thyroidectomy due to incidental thyroid malignancy, compared to 3 patients (1.51%) in Group 1. This included 13 patients in Group 2A, 13 in Group 2B, and 1 in Group 2C.

4. Discussion

Thyroid nodules are morphological changes that can be distinguished from normal thyroid tissue through ultrasound (USG) examinations. They occupy space within the parenchyma and have different consistencies. Thyroid nodules are more commonly seen in endemic regions and are one of the most frequently encountered conditions in clinical practice. Approximately 5% of women and 1% of men worldwide have palpable nodules. Ultrasound examinations reveal thyroid nodules in 10-68% of the population [1, 10, 11, 12, 13].A thyroid nodule can be noticed by the patient themselves, but more frequently, it is detected during physical examinations or through radiological imaging methods (such as neck ultrasound, PET/CT, CT, MRI, etc.). Nowadays with the increasing use of imaging methods for diagnostic and screening purposes for various reasons, there has been a notable rise in the number of thyroid nodules and consequently, thyroid cancers [14,15]. Some authors argue that the increase in the number of nodules, especially cancer cases, cannot be solely explained by the rise in imaging techniques [16, 17]. This is because the relative increase in cancer cases is observed not only in small-sized nodules but also in larger ones. Approximately 5-14% of thyroid nodules are malignant [1, 18]. Therefore, the medical history, physical examination, imaging, and cytological evaluations of patients with thyroid nodules should be conducted thoroughly and carefully. Regardless of how the diagnosis is made, as the detection rate of thyroid nodules increases, so do the uncertainties regarding the clinical approach to these nodules. This situation emphasizes the importance of understanding the malignancy risk associated with nodules detected in the preoperative period.

For the evaluation of incidentally detected or clinically noticed thyroid nodules, total neck ultrasound is the primary imaging method. In these ultrasound examinations, patients in the risk group undergo Fine Needle Aspiration Biopsy (FNAB) for cytological evaluation of the nodule. FNAB is the gold standard method for diagnosing nodules with high accuracy through a simple procedure [19, 20]. However, although FNAB can aid in distinguishing malignant from benign nodules, uncertain results can create clinical dilemmas, and pathologists cannot provide a clear diagnosis for approximately 30% of thyroid nodules for various reasons [21].

To standardize pathological interpretations, the Bethesda Reporting System, updated by the National Cancer Institute in 2023 [5], is utilized. The category IV diagnosis of FN within this reporting system is still defined as a gray area in clinical studies. In this category, distinguishing between benign and malignant disease is not possible cytologically. Various studies have shown that approximately 27-52% of lesions diagnosed as FN by FNAB are often malignant upon histopathological examination. The most frequently observed malignancy is Papillary Thyroid Carcinoma (PTC), followed by Follicular Thyroid Carcinoma (FTC) [22, 23]. The majority of such nodules (48-73%) are benign, meaning many patients are subjected to unnecessary diagnostic surgeries. Thyroid surgeries can lead to serious complications such as thyroid hormone imbalance, hypoparathyroidism, recurrent laryngeal nerve injury, bleeding, and infection, in addition to increasing hospitalization costs[24].

There is no complete consensus on the recommended treatment for Bethesda Category IV thyroid nodules, but the most commonly applied method, also included in the ATA guidelines [25], is hemithyroidectomy (HT). Recently, molecular tests for risk assessment have emerged to avoid unnecessary surgical interventions. However, these molecular tests are quite expensive and difficult to access.

Given that a significant portion of these nodules is benign after surgery, it is believed that this group of patients faces unnecessary surgical morbidity risks. On the other hand, if the final pathology result is malignant, the possibility of complementary thyroidectomy arises. The risks of surgical complications associated with secondary interventions (such as recurrent laryngeal and superior laryngeal nerve injuries, hypoparathyroidism, etc.) increase with complementary thyroidectomy.

Additionally, varying rates of thyroid malignancy based on geographic regions, the presence of Hashimoto's disease accompanying Bethesda category IV FN in patients, the existence of concurrent multinodular disease, and social factors such as patients' refusal to consider a second surgery raise the option of total thyroidectomy (TT) in patients classified as high-risk radiologically and clinically, despite being in the gray area cytologically.

This controversial situation and uncertainty highlight the need for research into preoperative assessment criteria that could be used to determine the overall malignancy risk of these nodules or the risk rates specific to clinics (such as geographic differences and hospitals located in regions with high cancer prevalence) and emphasize the necessity for treating patients based on these results [22, 26, 27].

Numerous studies in the literature have investigated demographic, clinical, and radiological predictive factors for malignancy in FN. Common and differing results have been reported, and the factors predicting malignancy risk in patients have not been fully established. Age, male gender, large nodule size, ultrasound characteristics, and cytological features have been reported as primary risk factors for identifying patients at risk of malignancy. However, variables determining malignancy in follicular neoplasms remain a topic of debate [28].

Among the predictive factors, ultrasound characteristics have been studied, with solid structure of the nodule, microcalcifications, or hypoechoic patterns being associated with malignancy [2]. In our study, all ultrasound variables believed to increase the risk of malignancy in nodules during the preoperative period were evaluated, and no differences in ultrasound characteristics were found between malignant and benign groups. Since all patients in our study were evaluated by the same radiology team, we believe that misleading factors related to the radiologist are at their lowest level. Consequently, we observed that ultrasound findings were not effective in distinguishing between benign and malignant FN. For thyroid nodules classified as EU-TIRADS 5, a decision for fine needle aspiration biopsy (FNAB) is typically made [29]. We attribute the primary reason for features increasing malignancy risk, or in other words, the EU-TIRADS category, not actually increasing malignancy risk to the frequent demonstration of EU-TIRADS 5 category features in benign nodules as well. In another study, similar to ours, no difference in ultrasound characteristics was found between benign and malignant follicular thyroid lesions [30]. Similarly, Sillery et al. demonstrated that the ultrasound characteristics of follicular adenomas and follicular thyroid carcinomas (FTC) are similar [31]. There are controversial results regarding additional potential ultrasound features associated with follicular malignancy, such as the absence or presence of a halo, hypoechogenicity or isoechogenicity, unclear borders, and the absence of cystic changes [22, 27, 31-33].

It is a well-known fact that the presence of a solid component in thyroid nodules increases the risk of malignancy. In contrast, the presence of a cystic component significantly decreases this risk. In our study, we also demonstrated that as nodule size increases, the rate of malignancy rises. We noted that the cystic nature of the nodule serves as an indicator that reduces the likelihood of malignancy. Interestingly, while the probability of cancer in solid nodules increases with nodule size, this is not the case for cystic nodules, where the risk of malignancy does not rise despite an increase in size.

Malignancy rates in FN show variations between clinics. These differing rates are influenced not only by clinical data but also by the demographic and ethnic characteristics of the patients. Bongiovanni et al. reported a malignancy rate of 26.1% in FN cases [34]. In another study by Kim et al., the malignancy rate was noted as 35.1% [28]. They attributed this higher rate compared to literature reports to ethnic differences. They mentioned that most previous studies were conducted in the United States, while in their own country, Korea, the prevalence of thyroid cancer is high. Similarly, another study conducted in Korea by Yim et al. reported a malignancy rate of 48% [35]. In another study, the malignancy rate in Bethesda Category IV nodules was found to be 48.9%. Additionally, incidental malignancy was detected in 30.7% of patients, leading to a total malignancy rate of 79.6% [36]. In our study, the malignancy rate among patients diagnosed with FN who underwent surgery was found to be 45.3%. This rate is higher than that reported in many studies in the literature. Similar to the studies from Korea, we attribute this high rate to the elevated prevalence of thyroid cancer in the region where the study was conducted.

In our study, incidental malignancy was observed outside the target nodule in 138 of the 364 patients (37.9%). In Group 1, the rate of incidental thyroid cancer was 34.1% (68/199 patients), while in Group 2 it was 42.4% (70/165 patients). In both groups, the most frequently observed histological type was micro-papillary thyroid cancer. Another study highlighting the regional differences affecting the incidence of thyroid cancer reported that 721 patients underwent surgery for FN, with 402 (55.7%) having total thyroidectomy (TT) and 319 (44.3%) having hemithyroidectomy (HT), resulting in a malignancy rate of 24% (176/721 cases). The patients in this study were operated on in two different regions. The malignancy rate was recorded as 34.9% in Sardinia and 18.9% in Campania. Additionally, the risk of malignancy was higher in those who underwent TT (31%) compared to those who had HT (16%). However, considering that the malignancy rate remains low even after routine TT, there is commentary suggesting that surgical interventions may signify "overtreatment" in many cases. The study states that Sardinia is an endemic goiter region, with a very high incidence of autoimmune diseases (especially Hashimoto's thyroiditis), which likely contributes to the observed higher malignancy rates. For these reasons, it is emphasized that when making surgical decisions, not only clinical and radiological data but also ethnic and regional factors may play a role in malignancy risk. This situation explains the prevalence of TT selection in endemic regions, a regional risk factor [37]. Other studies also highlight that the structure of at-risk populations and the clinical-pathological characteristics of cancer may vary significantly based on ethnic origin and geographic location [38].

In our study, 27 patients (16.36%) in Group 2 and 3 patients (1.51%) in Group 1 (who were found to have incidental thyroid malignancy) underwent complementary thyroidectomy. Bilateral total thyroidectomy (TT) was performed on 130 patients in Group 1 and 118 patients in Group 2, while unilateral thyroidectomy was performed on 69 patients in Group 1 and 47 patients in Group 2. The high rate of TT in our study can be attributed to the presence of hyperthyroidism in 60 patients (16.48%) (37 in Group 1 and 23 in Group 2) and hypothyroidism/Hashimoto's disease in 24 patients (6.59%) (12 in Group 1 and 12 in Group 2). Additionally, 17 patients (4.67%) had a family history of thyroid cancer (8 in Group 1 and 9 in Group 2), and one patient had previously been operated on for papillary thyroid cancer. Furthermore, ultrasound examinations revealed that bilateral thyroid nodules were present in 63.32% of patients in Group 1 and 55.76% in Group 2. The endemic nature of thy-

roid diseases and cancer in our region also plays a significant role in our broader surgical practices.

In a study, the most frequently encountered malignant pathologies in FN cases were identified as PTC (53.4%) and FTC (40.49%). Moreover, nearly one-third of the malignancies (37.7%) were fvPTC. The authors suggested that the high rate of fvPTC cases may be due to the possibility of misdiagnosis or incorrect diagnosis of truly malignant cases as a result of fine-needle aspiration biopsy (FNAB) [28]. These malignant cases were diagnosed correctly post-surgery due to the absence of tumor capsule and vascular invasion findings. In our study, the most common histological subtypes observed in the malignant group were micropapillary thyroid carcinoma in 48 patients (29%) and fvPTC in 57 patients (34.5%). In eight patients (4.8%), FTC was observed. When examining the pathological evaluations of the patients' subgroups (2A, 2B, 2C), the most common histological subtype in Group 2A was micropapillary thyroid carcinoma, in Group 2B it was fvPTC, and similarly in Group 2C it was also fvPTC.

A study investigating factors that help predict malignancy after preoperative FN diagnosis analyzed 368 thyroidectomy samples. The authors found that 60% of nodules with cytological nuclear changes associated with PTC were malignant [39]. In another study involving 98 FN cases, the malignancy rates for atypical and non-atypical FN were reported as 44.4% and 6.8%, respectively, thus supporting the predictive value of the presence of atypical FN [8]. In our study, there was no data related to nuclear atypia in cytological examinations, and thus, an assessment could not be made regarding this predictive risk factor. Due to the retrospective nature of our study, there are parameters with data deficiencies, which constitutes the most significant limitation of our research.

Another clinical variable investigated for predicting malignancy in FN is gender. Many studies have shown that male gender is significantly associated with a diagnosis of malignancy [40, 41]. In a study based on multivariable analyses, Najafian et al. indicated that male gender, a family history of thyroid cancer, and a history of head and neck radiation exposure are associated with malignancy in follicular neoplasms of the thyroid [30]. In our study, malignancy was detected in 42.7% of female patients and 55.3% of male patients. According to these findings, the rate of malignancy in male patients was significantly higher, similar to the literature. However, there was no statistically significant difference (p=0.051). Additionally, there was no statistically significant difference in the distribution of 17 cases with a family history of thyroid cancer between groups 1 and 2, and our study found that a family history of thyroid cancer was not a determining factor for predicting malignancy in FN.

None of our cases had a history of radiation exposure to the head and neck region. Considering that patient age could be another determinant in predicting the malignancy potential of FN cytology, the cases were evaluated according to age ranges. The group with the highest rate of malignancy was the youngest age group, 18-25 years. In the two youngest age ranges, 18-25 and 26-40 years, the number of malignant pathologies exceeded that of benign ones; however, this trend reversed in the 41-60 age range. This suggests that any prediction of malignancy with age might lie between these two groups. Additionally, studies highlighting that being under 45 years old is a risk factor for malignancy were also considered[30, 41]. Based on these data, a repeated chi-square analysis indicated that 160 cases were under 45 years old, while 204 cases were 45 years or older. Among those under 45, 88 (55%) cases were malignant, and 72 (45%) were diagnosed with benign pathologies. Among those over 45, 77 (27.7%) cases were malignant, and 127 (62.3%) cases were benign. The likelihood of FN cytology nodules being malignant was statistically significantly higher in cases under 45 years (p<0.001).

The literature presents conflicting results regarding nodule size and the risk of malignancy. Tuttle et al. reported that tumor sizes greater than 4 cm are associated with an increased risk of malignancy [42]. Schlinkert et al. emphasized that the risk of malignancy in follicular neoplasms is higher in larger tumors [41]. Another study showed that a tumor size greater than 2.1 cm increases the risk of malignancy [43]. In Lee KH et al.'s study, tumor size (>2.5 cm) and ultrasound findings suggestive of malignancy were proposed as determining factors [44], whereas Lee SH et al. found that only high TG levels and the presence of calcifications on ultrasound were significant predictive factors [27]. Overall, there are discussions about the utility of clinical characteristics, including nodule size, in predicting malignancy. According to one view, while the risk of PTC decreases with larger nodules, the risk of FTC increases as nodule size increases [45]. Recent studies suggest that nodule size in thyroid FN predicts malignancy potential [46]. This is consistent with the American Thyroid Association guidelines, which recommend total thyroidectomy for follicular lesions larger than 4 cm due to the increased risk of malignancy [47]. In contrast, some studies argue that there is no significant difference in nodule size between benign and malignant groups [27]. There are also studies that claim there is no relationship between increasing nodule size and malignancy rates [48]. In our study, when examining the relationship between nodule size and malignancy, it was observed that nodules 2 cm and smaller are frequently benign, while malignancy rates are higher in nodules between 2-4 cm and in those 4 cm and larger. Our findings parallel those of many studies in the literature. Differences in results from studies exploring the relationship between nodule size and malignancy risk may arise from variations in study populations and assessment criteria. According to authors who argue that nodule size is not proportional to malignancy risk, malignant thyroid nodules, especially undifferentiated types, may have a higher likelihood of growing faster than benign lesions. Furthermore, they are more likely to have a suspicious or malignant FNAB, which leads to earlier surgical intervention. In contrast, benign nodules are often monitored longer before surgery, during which time they may also grow. As in our study, authors who support the notion that the increase in nodule size is proportional to the increase in malignancy risk argue that the false-negative rate for FNAB increases with nodules larger than 4 cm [45].

The relationship between Hashimoto's thyroiditis and thyroid cancer remains a topic of debate [49, 50]. Studies by Rago et al. and Pu et al., which examined FN and Hürthle cell neoplasms together, showed that malignancy was not associated with Hashimoto's thyroiditis[32, 51]. In contrast to these studies, Zhang et al. suggested a significant association between Hashimoto's thyroiditis and the risk of PTC, reporting a much higher incidence of PTC in male patients with Hashimoto's thyroiditis [52]. In our study, all 33 patients with Hashimoto's thyroiditis underwent total thyroidectomy. Nineteen patients were in Group 1, and 14 were in Group 2. The frequency of malignancy in these patients was observed to be 42%, which is consistent with the overall malignancy rate. It was noted that Hashimoto's thyroiditis did not increase the risk of malignancy in nodules with FN.

Recently, molecular biomarkers such as BRAF, RAS, RET-PTC, or PAX8-PPARγ mutations are being researched for the diagnosis of thyroid nodules. BRAF mutations are observed in up to 83% of PTCs [53-55], while NRAS mutations are commonly found in FN [56]. In one study, NRAS mutations were observed in 22.3% of patients, with a higher prevalence of NRAS mutations in the malignant group (%13.8 vs. %30.4, p=0.013). Additionally, in the same study, multivariable analysis revealed that NRAS mutation was an independent risk factor for a malignancy diagnosis [28]. Similarly, Bae et al. reported that the overall malignancy rate in NRAS mutation cases was significantly higher compared to those without the mutation[57]. Fur-

thermore, many studies have demonstrated that immunohistochemical markers such as galectin-3, HBME1, and cytokeratin-19 improve the sensitivity and specificity in differentiating benign cases from malignant cases in nodules preoperatively. However, due to various reasons such as operator-dependent factors, differences in analytical methods, and the overlap between follicular adenomas and differentiated thyroid carcinomas, these markers have not gained widespread acceptance in clinical practice [58, 59]. In our study, we did not have data related to molecular and immunohistochemical markers, so we could not draw conclusions about the predictive effects of the existing markers.

In a study conducted by Najafian et al., it was found that despite some differences in the presentation characteristics of benign and malignant follicular thyroid nodules, independent preoperative variables for malignant follicular thyroid lesions included male gender, positive family history, history of thyroid cancer, and a history of head and neck radiation [30]. Conversely, being over 45 years of age, presenting with dysphagia or a sensation of pressure, having a nodule larger than 4 cm, accompanying hyperthyroidism, and the presence of multinodular goiter emerged as preoperative indicators for benign follicular thyroid lesions. The correct combination of all clinical indicators may assist in making preoperative decisions for patients with follicular lesions. In our study, patients with malignancy were often younger and male. It was observed that malignancy increased in lesions measuring 2 cm or larger. There was no statistically significant difference in the presenting complaints between Groups 1 and 2. Our study observed that changes in thyroid function tests did not differ between benign and malignant groups. However, literature indicates that hyperthyroidism is more common in benign follicular thyroid lesions [30]. Given that hyperfunctioning thyroid nodules have a higher likelihood of being hot nodules, it is not surprising to observe such a relationship [60].

Recently, a gene expression classifier (Afirma) has been found to be quite useful in distinguishing between benign and malignant nodules in follicular lesions. This gene expression classifier has been reported to have a sensitivity of 90% for both indeterminate lesions and FN. The specificity and negative predictive value for FN are 49% and 94%, respectively. However, as mentioned above, access to these tests is often limited due to cost constraints. This situation highlights the search for other predictive factors that could potentially replace these molecular tests, which is a central theme of our study.

According to literature data, the increase in FN diagnoses has led to more thyroid surgeries, revealing a relatively low malignancy rate (MR) associated with FN (10-40%) [4, 9, 44]. Furthermore, neither preoperative ultrasound features, molecular markers, nor intraoperative pathology consultations have sufficient sensitivity to predict malignancy [61]. On one hand, total thyroidectomy (TT) may increase the need for medication and the risk of surgical complications due to excessive surgical intervention; on the other hand, hemithyroidectomy (HT) might not require medication or may only require low doses, with a lower risk of surgical complications, although it may sometimes necessitate complementary thyroidectomy. These two extremes represent the surgical treatment options for managing FN. Despite numerous studies in the literature, management guidelines remain debated; endocrinologists or head and neck surgeons are divided into those who support routine TT and those who oppose it. Additionally, surgical treatment options for FN vary between institutions and even among surgeons within the same institution. Current evidence confirms that patients with FN should be better evaluated preoperatively to avoid unnecessary diagnostic surgery.

The differences in malignancy rates in the literature suggest that the biological behavior of the disease may vary by geographical region. Demographic, clinical and radiological predictive risk factors associated with patients yield different results across studies. Currently, the use of molecular tests recommended for FN is limited. Due to cost concerns and issues with institutional access, these tests have not yet been adopted into routine practice. Furthermore, discussions continue regarding frozen section pathology examinations performed during surgery and how treatment strategies should be determined accordingly. In light of all this data, many factors must be considered when selecting the type of surgery for patients with FN. It should be noted that TT might be overtreatment in cases of FN where the risk of malignancy is relatively low. Conversely, performing HT without considering possible risk factors could lead to additional surgical interventions, increasing costs and surgical complications. While a more conservative surgical approach is recommended for FN patients, there is a need for multicenter, multifactorial analyses based on prospective randomized studies aimed at reducing unnecessary diagnostic surgeries and increasing preoperative diagnostic accuracy.

5. Conclusion

According to the results of our study, the risk of malignancy in FN cases increases in males, nodules larger than 2 cm, and younger age groups. Our data indicate that the malignancy risk in FN is 45.3%. Additionally, the incidental thyroid cancer rate outside of the targeted FN nodule was found to be 37.9%. These rates are higher than those reported in the literature, likely due to the high prevalence of thyroid cancer in our region. Furthermore, the presence of concurrent Hashimoto's disease, the detection of multiple nodules on ultrasound examinations and a history of thyroid cancer in some patients have led to a more frequent preference for total thyroidectomy (TT) in our surgical choices. However, it has been observed that these variables do not increase the risk of malignancy in FN.

Statement of ethics

Ethical approval was obtained from the Başkent University School of Medicine with the number KA 22/125.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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