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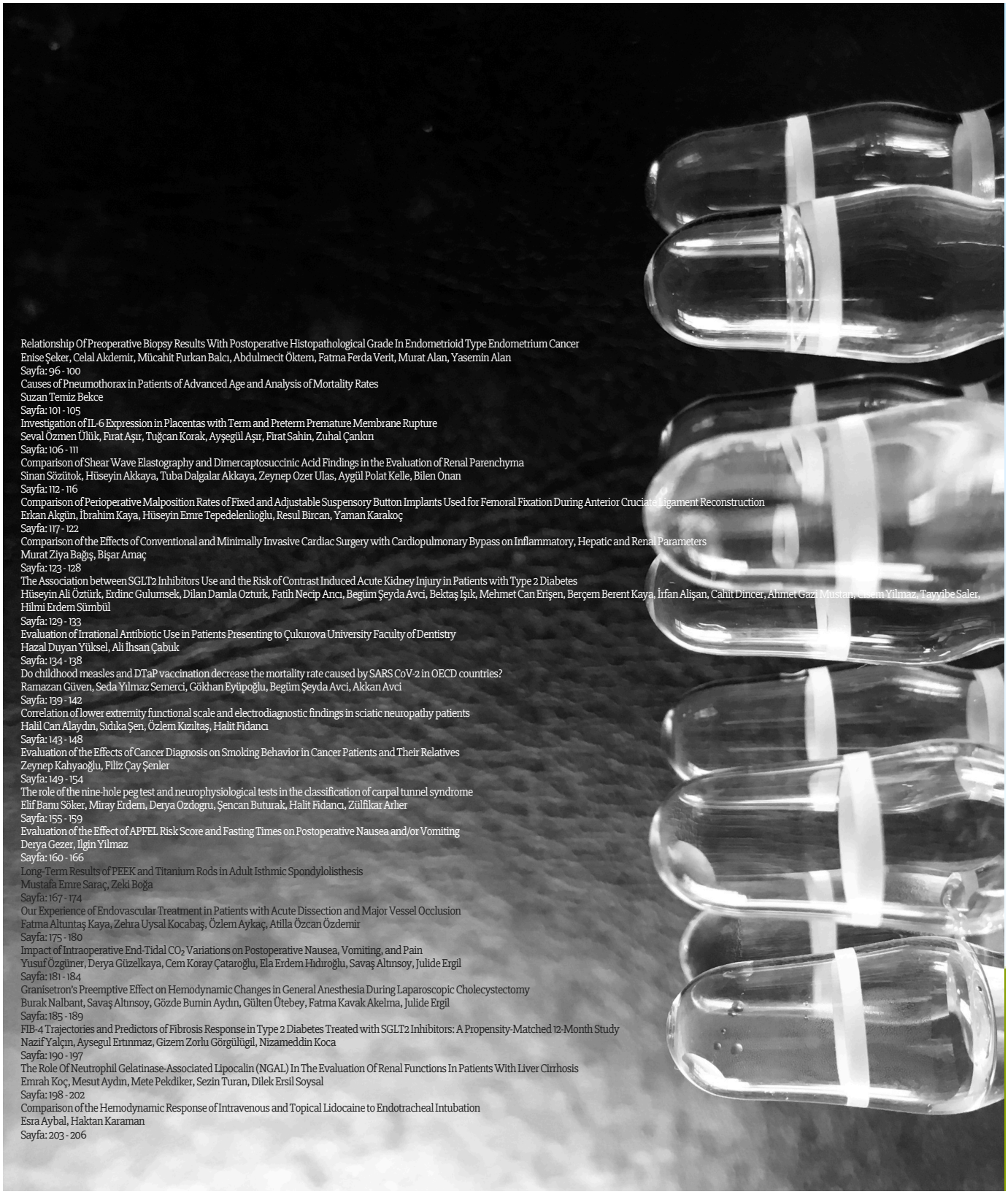

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ABSTRACTED & INDEXED

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BASE
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ASOS Indeks
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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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ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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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http://www.icmje.org/recommendations/browse/roles-and-responsibilities/responsibilities-in-the-submission-and-peer-peview-process.html
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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

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• In case presentations, "informed consent" should be obtained from the patients.
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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.
Editors should not publish reviewers' comments without the permission of reviewers and authors. If journal policy will protect authors against the reviewer's identity and comments are not signed, that identity should not be disclosed to the author or others without the express written consent of the reviewers.
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).
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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.

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- When publishers will not allow OA on the funder's terms, funder policies should require grantees to seek another publisher.
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Article text should start from the second page.
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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References should be written on a separate page and should be numbered according to the order of transition.
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.
If there are more than two consecutive sources, the first and last ones should be given a "-" sign:
References should contain the full surnames of the authors and the first letters of their names.
If the number of writers in the source is 3 or less, all authors should be mentioned. the source should be written.
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Authors are responsible for the correctness of references and spelling.
Manuscripts and punctuation marks must comply with the following examples.
The source is a magazine; The author should be written in full capitalization, and the first name should be written as first letter and larger. Title of article. The journal is abbreviated to Index Medicus. Year: Volume: First page number-Last page number
If the source is a book; Name (s) of the surname of the author (s). The name of the book. What is the pressure? Publication Place: Printing House, Publication Year.
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If the website is shown as source; The name of the Web site. (accessed date)
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Tables:
1. Tables should be written on a separate page with a single line spacing.
2. Each table should have number and descriptive information above it.
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4. When previously printed or electronically published tables are used, written permission must be obtained from both the author and the printer and this must be sent to the editor of the journal by fax or mail.
5. Transverse and longitudinal lines should not be used in the table, only a straight line should be drawn at the top and bottom.
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7. The explanations of the figures should be written at the end of the file to which the manuscript is sent.
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9. The pictures / photos should be colored, the details should be clearly visible and clear.
10. Figures, pictures / photos are separate. jpg file should be added to the system.
11. Image and photo files should not be less than 100 pixel / inch, 8 cm wide and 300dpi.

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ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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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ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS I

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ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS II

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Relationship of Preoperative Biopsy Results with Postoperative Histopathological Grade in Endometrioid Type Endometrium Cancer

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Abstract

Aim: To assess the concordance between preoperative endometrial biopsy and final postoperative histopathological findings in patients with endometrioid-type endometrial cancer, and to identify factors associated with diagnostic discrepancies.

Methods: This retrospective study included 134 patients who underwent surgery between 2005 and 2018 following a preoperative diagnosis of endometrioid-type endometrial cancer at a tertiary center. Demographic, clinical, and histopathological data were reviewed. Concordance between preoperative biopsy and final pathology was evaluated using Cohen's kappa coefficient. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Results: A statistically significant correlation was observed between preoperative and final tumor grades ($p < 0.001$). In 35.8% of patients (n = 48), the final pathology revealed a higher grade than the initial biopsy. Grade 3 tumors demonstrated the highest diagnostic accuracy (89.5%), while Grades 1 and 2 showed an overall accuracy of 66.0%. Tumor size greater than 2 cm and lymph node metastasis were significantly associated with grade upgrading ($p = 0.014$ and $p = 0.004$, respectively).

Conclusions: Preoperative biopsy alone may not be sufficient for accurate risk stratification in patients with endometrial cancer. Tumor upgrading was significantly associated with adverse prognostic indicators such as larger tumor size and nodal involvement. A multimodal diagnostic approach is recommended, particularly in cases initially classified as low-grade.

Keywords: *Endometrial Cancer; biopsy; histopathology; grade concordance; lymph node involvement*

1. Introduction

Endometrial cancer, the most prevalent gynecological malignancy in developed nations, has been experiencing a steady rise in incidence.[1,2] Several contributing factors have been identified, including obesity, dietary changes, an aging population, delayed menopause, and diabetes.[3] Over 75% of endometrial cancer cases are diagnosed at an early stage, primarily due to symptoms such as abnormal vaginal bleeding.[4,5]

Despite the high rate of early detection, the continued increase in incidence and mortality highlights persistent challenges in achieving accurate diagnosis and providing optimal treatment. Standard diagnostic procedures include pipelle endometrial biopsy, dilatation and curettage (D&C), and hysteroscopic evaluation.[5-7] In general, surgery is the first-line treatment unless there is extrauterine pelvic disease that precludes surgical intervention.

The primary surgical treatment for suspected early-stage endometrial cancer is hysterectomy with bilateral salpingo-oophorectomy, with or without lymph node dissection. In certain cases, adjuvant therapies such as chemotherapy and/or radiotherapy may be considered based on recurrence or mortality risk.[8-10] Patients are stratified into risk categories based on histopathological evaluation. Preoperative biopsy plays a pivotal role in predicting the final pathology result, which significantly

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influences surgical decision-making. The triple rating (grade) system developed by the International Federation of Gynecology and Obstetrics (FIGO) is commonly used to classify endometrioid-type endometrial cancer. Extensive research has demonstrated the prognostic importance of tumor grade, with Grade 1 tumors typically associated with favorable outcomes, and Grade 3 tumors linked to poor prognosis.[9,10] According to recent ESMO-ESGO-ESTRO consensus guidelines, preoperative risk stratification and histological grading are essential for tailoring surgical staging and adjuvant treatment strategies.[11]

This study aimed to evaluate the concordance between preoperative endometrial biopsy and final postoperative histopathological findings in patients with endometrial cancer. It also assessed whether the surgical treatment based on preoperative biopsy was appropriate by examining if it was excessive, sufficient, or insufficient when compared with the final pathology results. In addition, the study investigated potential factors that may contribute to discrepancies, including tumor grade, tumor size, depth of myometrial invasion, cervical stromal invasion, and lymph node involvement.

2. Materials and Methods

A retrospective analysis was conducted on patients with endometrioid-type endometrial cancer who underwent surgery between January 2005 and December 2018. Ethical approval for the study was obtained from the institutional review board of Istanbul Training and Research Hospital. Patients diagnosed with non-endometrioid-type endometrial cancer in the final postoperative pathology or those who did not undergo surgical staging were excluded. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed variables are presented as mean ± standard deviation, while categorical variables are expressed as frequencies and percentages. Group comparisons were made using the Chi-square test or Fisher's exact test, as appropriate.

The strength of agreement was interpreted based on the value of Cohen's kappa coefficient, where values below 0.20 indicated slight agreement, 0.21 to 0.40 indicated fair agreement, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and values above 0.80 were considered to indicate almost perfect agreement.[12] Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. A p-value of < 0.05 was considered statistically significant.

3. Results

A total of 134 patients diagnosed with endometrioid-type endometrial cancer based on preoperative biopsy underwent hysterectomy and bilateral salpingo-oophorectomy. Patient ages ranged from 32 to 81 years, with a mean age of 59.3 ± 9.1 years. Parity ranged from 0 to 12, with an average of 2.5 ± 2.1 (median: 2).

According to preoperative biopsy, 63.4% (n = 85) of patients were classified as Grade 1, 26.1% (n = 35) as Grade 2, and 10.5% (n = 14) as Grade 3. Lymph node dissection was performed in 86.6% of patients (n = 116). Among them, 59.0% (n = 79) underwent pelvic dissection alone, while 27.6% (n = 37) underwent both pelvic and para-aortic dissection. No lymphadenectomy was performed in 13.4% (n = 18) of cases.

Lymph node involvement was detected in 11 patients (9.5%). Of these, 4 had isolated pelvic node metastasis, and 7 had both pelvic and para-aortic metastases. All patients who underwent para-aortic dissection also had pelvic node dissection.

Table 1

Postoperative Pathology Results

	Number (n)	Percent (%)
Tumor Size		
• 2 Cm ≤	38	28.4
• 2 Cm >	96	71.6
Myometrial Invasion		
• % 50 <	84	62.7
• % 50 ≥	50	37.3
LVS Invasion		
• Invasion (+)	21	15.7
• Invasion (-)	113	84.3
Cervical Invasion		
• Invasion (+)	17	12.7
• Invasion (-)	117	87.3
Total	134	100

LVS: Lymphovascular Space

Table 2

Relation of Preoperative and Postoperative Grade Results

Preoperative Grade	Postoperative Grade							
	Grade 1		Grade 2		Grade 3		NE	
	n	%	n	%	n	%	n	%
Grade 1	42	95,5	36	54.5	3	21.4	4	40.0
Grade 2	2	4.5	28	42.4	4	28.6	1	10.0
Grade 3	0	0.0	2	3.0	7	50.0	5	50.0

Kappa:0.393; p<0.001 NE: Non-Endometrioid Type

Table 3

Preoperative Grade Sensitivity, Specificity PPD and NPD

	Preoperative Grade					
	Grade 1		Grade 2		Grade 3	
	%	CI	%	CI	%	CI
Sensitivity	95.5	89.3-101.6	42.4	30.5-54.3	50.0	30.0-70.0
Specificity	52.2	41.9-62.5	89.7	82.5-96.9	98.2	95.7-100.7
PPV	49.4	38.8-60.0	80.0	66.7-93.3	85.7	67.4-104.0
NPV	95.9	90.4-101.5	61.6	52.0-71.2	90.0	84.6-95.4
	66.0		66.0		89.5	

PPD: Positive Predictive Value NPD: Negative Predictive Value CI: Confidence Interval

Table 4

The Relationship Between Preoperative Grade and Other Postoperatively Determined Features

	Preoperative Grade						
	Grade 1		Grade 2		Grade 3		
	n	%	n	%	n	%	p
Tumor sizes							
• 2 Cm ≤	22	25.9	13	37.1	3	21.4	0.384
• 2 Cm >	63	74.1	22	62.9	11	78.6	
Myometrial Invasion							
• < 50 %	54	63.5	23	65.7	7	50	0.569
• ≥ 50 %	31	36.5	12	34.3	7	50	
LVS Invasion							
• (+)	10	11.8	7	20	4	28.6	0.198
• (-)	75	88.2	28	80	10	71.4	
Cervical Invasion							
• (+)	9	10.6	3	8.6	5	35.7	0.055
• (-)	76	89.4	32	91.4	9	64.3	
LN Metastasis °							
• (+)	7	9.7	2	6.5	2	15.4	0.661
• (-)	65	90.3	29	93.5	11	84.6	
Stage *							
• Stage 1	66	77.6	29	82.9	7	50	
• Stage 2	8	9.4	2	5.7	3	21.4	
• Stage 3	9	10.6	4	11.4	2	14.3	
• Stage 4	2	2.4	0	0	2	14.3	
Total	85	100	35	100	14	100	

** Chi-square analysis could not be performed. °A total of 116 patients who underwent lymph node dissection. LVS: Lymphovascular Space, LN: Lymph Node*

Final postoperative pathology confirmed the endometrioid type in 92.5% of patients (n = 124). The remaining 7.5% (n = 10) were diagnosed with non-endometrioid subtypes, including 4 serous, 1 mixed, 1 undifferentiated, and 4 carcinosarcomas.

Tumor characteristics revealed that 71.6% (n = 96) of patients had tumors larger than 2 cm. Lymphovascular space invasion (LVSI) was present in 15.7% (n = 21), and cervical stromal invasion was observed in 12.7% (n = 17) (Table I). The majority of patients were diagnosed at an early stage: 53.7% (n = 72) were Stage IA, 22.4% (n = 30) Stage IB, 9.7% (n = 13) Stage II, 11.2% (n = 15) Stage III, and 3.0% (n = 4) Stage IV.

Postoperative histopathological examination revealed grade upgrading in 35.8% of cases (n = 48). Among these, 36 patients (26.9%) were upgraded from Grade 1 to Grade 2 or 3, and 7 patients (5.2%) were upgraded directly to Grade 3. Only 4 patients were downgraded, none of whom were downgraded from Grade 3 to Grade 1.

Concordance between preoperative and postoperative grades was evaluated using Cohen's kappa coefficient, yielding a value of 0.383 ($p < 0.001$), indicating fair agreement (Table II).

Table 5

The Relationship Between Lymph Node Involvement and Postoperative Grade

	LN Involvement (+)		LN Involvement (-)		p
	n	%	n	%	
Preoperative Grade					
• Grade 1	7	63.6	65	61.9	
• Grade 2	2	18.2	29	27.6	0.661
• Grade 3	2	18.2	11	10.5	
Postoperative Grade*					
• Grade 1	0	0.0	35	33.3	
• Grade 2	4	36.4	54	51.4	
• Grade 3	7	63.6	16	15.2	
Total	11	100	105	100	

**Chi-square analysis could not be performed LN: Lymph node*

Table 6

Upgrade of Grade and Relationship with Other Pathology Outcomes

	Preoperative & Postoperative Grade				
	Non-Upgrade		Upgrade		
	n	%	n	%	P
Tumor Size					
• 2 Cm ≤	27	37.5	8	16.7	0.014
• 2 Cm >	45	62.5	40	83.3	
Myometrial Invasion					
• < 50 %	49	68.1	28	58.3	0.277
• ≥ 50 %	23	31.9	20	41.7	
LVS Invasion					
• Invasion (+)	9	12.5	8	16.7	0.521
• Invasion (-)	63	87.5	40	83.3	
Cervical Invasion **					
• Invasion (+)	9	12.5	3	6.3	0.358
• Invasion (-)	63	87.5	45	93.8	
LN Involvement **°					
• LN Involvement(+)	1	1.7	8	18.2	0.004
• LN Involvement(-)	58	98.3	36	81.8	
Stage					
• Stage 1	60	83.3	35	72.9	
• Stage 2	8	11.1	2	4.2	
• Stage 3	4	5.6	9	18.8	
• Stage 4	0	0.0	2	4.2	
Total	72	100.0	48	100.0	

**Patients with preoperative Grade 1 and Grade 2 are included (n:120).*
***Fisher exact, °Patients who underwent lymph node sampling were included (n:103).*

The sensitivity of preoperative biopsy for detecting Grade 1 tumors was 95.5% (95% CI: 89.3–101.6), with a negative predictive value of 95.9% (95% CI: 90.4–101.5). For Grade 3 tumors, sensitivity was 50.0% (95% CI: 30.0–70.0) and specificity was 98.2% (95% CI: 95.7–100.7). The lowest diagnostic sensitivity was

observed for Grade 2 tumors (42.4%, 95% CI: 30.5–54.3), with a negative predictive value of 61.6% (95% CI: 52.0–71.2). The highest accuracy rate was found in Grade 3 cases (89.5%) (Table III).

No statistically significant association was found between preoperative tumor grade and myometrial invasion (p = 0.569), lymph node metastasis (p = 0.661), LVSI (p = 0.198), cervical invasion (p = 0.055), or tumor size (p = 0.384). When preoperative grade was compared with FIGO stage, 77.6% of patients with Grade 1 tumors were Stage I, while 50% of those with Grade 3 tumors were also Stage I. Due to the absence of Grade 2 patients in the Stage IV group, statistical analysis for that subgroup could not be performed (Table IV).

When final pathology grade was compared with lymph node status, 63.6% of patients with node-positive disease were classified as Grade 3. Conversely, 63.6% of patients with lymph node metastasis had been initially graded as Grade 1 on preoperative biopsy, although many of these cases were subsequently upgraded in the final pathology (Table V).

A significant association was observed between grade upgrading and both tumor size greater than 2 cm (p = 0.014) and lymph node metastasis (p = 0.004). No significant relationship was found between grade upgrading and myometrial invasion (p = 0.277), cervical invasion (p = 0.358), or LVSI (p = 0.521) (Table VI).

4. Discussion

Endometrial cancer is the most common gynecological malignancy in developed countries. Its incidence continues to increase due to aging populations and lifestyle-related factors such as obesity and diabetes.[1-3] Although most cases are diagnosed at an early stage and generally carry a favorable prognosis, the rising incidence and mortality rates point to ongoing challenges in achieving accurate diagnosis and optimal treatment.[2] While early-stage detection is often prompted by symptoms such as abnormal uterine bleeding, accurate preoperative staging is essential to determine the most appropriate surgical and adjuvant treatment strategies.

Preoperative endometrial biopsy, typically performed using pipelle or dilatation and curettage (D&C), is widely accepted for estimating tumor grade and guiding surgical planning.[6] However, biopsy samples may not always capture the full histological heterogeneity of the tumor, potentially resulting in the underestimation or overestimation of tumor grade. In our study, we observed a weak but statistically significant correlation between preoperative biopsy and final histopathological grade. The diagnostic accuracy was highest for Grade 3 tumors (89.5%) and substantially lower for Grades 1 and 2 (66.0%).

Lago et al. demonstrated that concordance between biopsy and final pathology was highest in Grade 3 tumors (89.8%) and lower in Grade 1 (74.7%) and Grade 2 (73.2%) tumors.[14]. Our results showed a comparable pattern, with Grade 2 being the most frequently discordant category (73.1%). These discrepancies may be due to sampling limitations, particularly in tumors exhibiting focal solid growth or histological heterogeneity.

A significant association was observed between grade upgrading and both tumor size > 2 cm (p = 0.014) and lymph node metastasis (p = 0.004). No significant relationship was found between grade upgrading and myometrial invasion (p = 0.277), cervical invasion (p = 0.358), or LVSI (p = 0.521). These findings are summarized in Table VI, which presents the relationship between grade upgrading and various pathological features. They are consistent with previous reports indicating that tumor size and nodal involvement are key markers of aggressiveness in endometrial cancer.[13,15] Goksedef et al. similarly noted that discrepancies between biopsy and final pathology were more common in cases with larger tumors and deeper myometrial invasion.[15] Likewise, Lee et al. demonstrated a strong association between higher tumor grade and lymph node metastasis.[13]

A notable finding in our study was that 63.6% of patients with lymph node metastasis had been initially classified as Grade 1 based on preoperative biopsy. This suggests that relying solely on preoperative biopsy grade may underestimate true oncologic risk. Even among patients considered low-risk, comprehensive surgical staging including lymph node evaluation may be warranted. Additional preoperative assessment tools, such as magnetic resonance imaging (MRI) or intraoperative sentinel lymph node mapping, should be considered to improve risk stratification and optimize surgical planning.[16]

Our study also had limitations. Statistical analysis for Stage 4 patients could not be performed due to the absence of preoperative Grade 2 cases in this subgroup. This limitation may be related to referral patterns or selection bias inherent in retrospective study designs. Future multicenter prospective studies with larger sample sizes are needed to further explore the relationship between biopsy grade and final pathology, particularly in advanced-stage disease.

Although preoperative biopsy remains a valuable diagnostic tool, it should not be used in isolation. An integrated approach that combines histological evaluation, imaging, and intraoperative findings is essential to enhance diagnostic precision and guide individualized treatment decisions.

In conclusion, while preoperative endometrial sampling provides important preliminary information, its limited predictive value, particularly in low-grade tumors, underscores the need for supplementary diagnostic strategies. Prospective studies that incorporate radiologic and molecular data alongside biopsy results are essential to improve preoperative assessment in patients with endometrial cancer.

5. Conclusion

This study demonstrated that the concordance between preoperative endometrial biopsy and final histopathological findings in endometrioid-type endometrial cancer was limited, particularly for Grade 1 and 2 tumors. While preoperative biopsy remains a valuable diagnostic tool, it may not accurately reflect the final pathology in a significant proportion of patients. Notably, 63.6% of patients with lymph node metastasis were initially classified as Grade 1, highlighting the potential for risk underestimation.

These findings emphasize the need to incorporate additional diagnostic modalities, such as advanced imaging and intraoperative assessment, into the preoperative evaluation process. Relying solely on biopsy results may lead to inappropriate treatment decisions, including inadequate surgical staging. To improve risk stratification and optimize clinical outcomes, future research should focus on prospective, multicenter studies that integrate histopathological data with radiologic and molecular assessment tools.

Statement of ethics

Ethical approval was obtained from the Istanbul Training and Research Hospital Clinical Research Ethics Committee. (Date:18.01.2019/No:1642).

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

Concept (EŞ, CA), Design (EŞ, CA), Data Collection and/or Processing (EŞ, CA, FFV), Analysis and/or Interpretation (EŞ, CA, FFV)

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Causes of Pneumothorax in Patients of Advanced Age and Analysis of Mortality Rates

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Abstract

Aim: Spontaneous pneumothorax (SP) primarily affects young males but typically presents as a secondary condition in older adults. Secondary spontaneous pneumothorax (SSP) is a life-threatening condition that requires urgent intervention, often arising due to underlying chronic pulmonary diseases. This study aims to evaluate the etiological factors, clinical characteristics, treatment modalities, and mortality associated with SSP in patients aged 60 years and older based on current literature.

Methods: This study was conducted by retrospectively analyzing the outcomes of patients aged 60 and older who were followed up for SSP between October 2022 and July 2024.

Results: A total of 60 patients met the inclusion and exclusion criteria. The mean age was 72.03 ± 8.5 years (range: 60–91). Comorbidities were present in 54 patients (90%), while underlying pulmonary diseases were identified in 31 cases (51.66%). Conservative management was employed in six patients (10%), whereas 55 patients (91%) underwent tube thoracostomy. Pleurodesis was performed in 12 patients (20%), significantly reducing pneumothorax recurrence (p=0.001). Imaging revealed a significant association between bullous lung structures and pneumothorax recurrence (p = 0.008). Pneumonia was diagnosed in 35% of cases, and 13 patients with pneumonia had a statistically significant association with mortality (p< 0.001).

Conclusions: Secondary spontaneous pneumothorax is a life-threatening condition requiring timely intervention, particularly challenging in elderly patients. Data indicate that underlying lung disease and bullous structures on imaging increase the risk of pneumothorax recurrence. Prognostic factors associated with mortality include intensive care needs, complications, and pneumonia, highlighting their significance in management outcomes.

Keywords: *Advanced age; mortality; secondary spontaneous pneumothorax; secondary spontaneous pneumothorax*

1. Introduction

Pneumothorax, defined as the accumulation of air in the pleural space resulting from the partial or complete collapse of lung parenchyma, is classified as spontaneous, post-traumatic, and iatrogenic.[1,2] Secondary spontaneous pneumothorax (SSP) accounts for 10% of spontaneous pneumothorax (SP) cases.[3] Two distinct age peaks are observed in the age distribution of pneumothorax cases: the first occurs in young patients, while the second appears in the elderly population.[4] Primary spontaneous pneumothorax (PSP) is more common in younger individuals, whereas SSP is typically associated with underlying pulmonary diseases in older patients.[5] Smoking, tall stature, and being over 60 years of age increase the risk of PSP recurrence by up to 54% within four years.[6,7] Risk factors for SSP recurrence include age, pulmonary fibrosis, and emphysema.[7,8]

According to the guidelines of the British Thoracic Society (BTS) and the American College of Chest Physicians (ACCP), hospitalization is recommended for patients with spontaneous pneumothorax (SP), and intervention is required in cases where the pneumothorax exceeds 1 cm at the hilum or 2 cm at the apex.[9,10]

The presence of comorbidities in the elderly, complications related to pulmonary diseases, and impaired cardiopulmonary function complicate treatment. These factors may also lead to an increased risk of intensive care unit (ICU) admission, intubation, and mortality.[11] Therefore, in elderly patients, non-surgical treatment methods, such as chemical pleurodesis, are generally preferred.[12]

This study aims to evaluate the presence of underlying lung diseases in patients aged 60 and above with SSP, assess the development of complications during follow-up, and identify mortality and prognostic factors.

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2. Materials and Methods

This retrospective descriptive study was approved by the Non-Interventional Clinical Research Ethics Committee (Date: July 30, 2024, Decision No: 144). The study was conducted in compliance with the Declaration of Helsinki of the World Medical Association. Patients aged 60 years and older evaluated for pneumothorax between October 2022 and July 2024 were included. A total of 105 patients were assessed during the study period.

Sixty patients who met the inclusion and exclusion criteria were enrolled in the study. The study evaluated the following parameters for the patients: demographic characteristics, comorbidities, existing pulmonary diseases, number of pneumothorax episodes, the side of the pneumothorax, treatment approaches, the number of patients requiring chest tube placement, duration of chest tube placement, coexistence of pneumonia during pneumothorax, length of hospital stay, need for intensive care admission, length of stay in intensive care, and mortality rates. Eligible patients were managed conservatively, while tube thoracostomy was performed for those with an increase in pneumothorax size.

Patients who developed pneumothorax due to penetrating or cutting injuries, firearm injuries, trauma, assault, or iatrogenic causes were excluded from the study. Patients who passed away after discharge were not included in the mortality section. A total of 45 patients with incomplete parameters were excluded from the study.

2.1. Statistical analysis

The statistical analyses of the data were conducted using IBM SPSS (version 26.0), TURCOSA (www.turcosa.com.tr), and the R programming language (version 4.3.0, www.r-project.org). The relevant software programs were used in combination, depending on the type of analysis and specific requirements. Categorical variables were summarized using frequencies and percentages. The normality of the distribution of numerical variables was assessed using both graphical methods (e.g., histograms, box plots, Q-Q plots) and analytical approaches (e.g., Shapiro-Wilk normality test). Comparison of scale scores between groups was performed using the Student's t-test and One-Way Analysis of Variance (ANOVA) tests. When the assumption of normal distribution was not met, the Mann-Whitney U test and Kruskal-Wallis tests were used. For comparisons between groups in terms of categorical variables, Chi-Square tests (e.g., Pearson, Fisher, etc.) were applied. Correlations between variables were examined using Pearson or Spearman correlation coefficients, depending on the normality assumption. A p-value of <0.05 was considered statistically significant for all analyses.

3. Results

During the study period, 105 patients aged 60 years and older who were monitored due to SSP, were evaluated. Forty-five patients were excluded for not meeting the study's inclusion criteria, leaving a total number of 60 patients in the final analysis. Among these, 51 (85%) were male, and 9 (15%) were female. The mean age was 72.03 ± 8.5 years, with female patients having a higher average age than male patients.

In 51.66% of cases, patients had underlying pulmonary conditions, including chronic obstructive pulmonary disease (COPD), asthma, parenchymal lung diseases, and small airway diseases. Additionally, 90% of patients had comorbidities, such as hypertension, diabetes mellitus, cardiovascular disease, neurological disorders, and renal disease (Table 1).

In the study, 6.66% of the patients were diagnosed with lung cancer. Extrapulmonary malignancies were noted as lymphoma, pancreatic cancer, laryngeal cancer, hypopharyngeal cancer, and cranial-site cancer. These were identified in 15 of the evaluated cases. In 20% of the patients, pleural effusion was observed on the side of the pneumothorax, with exudative fluid detected in eight patients. Pneumothorax was found on the right side in 32 patients. Mortality was observed in 16 patients (Table 1).

Thoracic imaging evaluations revealed the presence of bullous structures in the parenchyma in 32 patients (53.33%), all of whom were male (p<0.001). On the side where pneumothorax was detected, pleural fluid was observed in 12 patients. There was no statistically significant difference between genders (p=0.857). Among the cases with pleural fluid, 4 (6.66%) were transudative, and 8 (13.33%) were exudative. When evaluated according to the side of SSP detection, no statistically significant difference was found (p=0.885) (Table 1).

Table 1

Demographic characteristics

	Mean±SD (min-max)
Age (average, years)	72.03±8.05 (60-91)
Female (n=9)	79.33 ± 9.47 (65-91)
Male (n=51)	70.74 ±7.12 (60-85)
	Total (n=60) (n, %)
Concomitant lung disease	31 % 51.66
Lung cancer	4 % 6.66
Extrathoracic cancer	15 % 25
Comorbid condition	54 % 90
Anticoagulant	31 % 51.66
Patients with pleural fluid association on the side of pneumothorax	12 % 20
Transudate	4 % 6.66
Exudate	8 % 13.33
Pneumothorax side	
• left	28 % 46.66
• right	32 % 53.33
Mortality	16 % 26.66

Table 2

The assessment of bullous structures on chest computed tomography

	pulmonary bullae structure	p value
Number of pneumothorax attacks		
• first attack	21 % 35	0.008
• second attack	5 % 8.33	
• third attack	3 % 5	
• four or more attacks	3 % 5	
Concomitant lung disease	25 % 41.66	<0.001
Lung cancer	1 % 1.66	0.511
Extrathoracic cancer	7 % 11.66	0.550
Mortality	4 % 6.66	0.008

A total of 32 patients showed the presence of bullous structures in thoracic imaging. The presence of bullous structures in the parenchyma were more frequently observed in patients with a history of their first pneumothorax attack (p=0.008). Among patients with underlying lung disease, 41.66% had bullous structures (p<0.001). Four of the deceased patients had bullous structures on their thoracic computed tomography (p=0.008) (Table 2).

When examining the treatment approach and management process in patients diagnosed with SSP, it was found that 6 out of 60 patients (10%) were followed up with conservative treatment. A patient who experienced a second attack of SSP, managed with oxygen therapy, was later treated with tube thoracostomy during follow-up. The number of patients followed up with tube thoracostomy was determined to be 55 (91.66%) (p=0.697). Tube thoracostomy was performed on 45 patients (75%) during the first pneumothorax attack. When comparing patients who underwent tube thoracostomy about mortality, no statistically significant difference was observed (p=0.725) (Table 3).

The average total hospital stay was 17.83 days (p=0.471).

The average duration of chest tube placement was 9.65 days (p=0.025). In cases monitored in the ICU, the average duration of chest tube placement was found to be 8.58 days (p=0.819) (Table 4).

The number of patients monitored with a Heimlich valve was recorded as 3 (5%). The number of patients who underwent pleurodesis was 12 (20%), 6 of whom (10%) received pleurodesis during their first pneumothorax attack. One patient underwent autologous blood patch pleurodesis, and 11 patients underwent pleurodesis with talc powder. No mortality was observed during the follow-up of patients who underwent pleurodesis (p=0.025). The number of patients followed in the intensive care unit was 31 (51.66%), 28 of whom (46.66%) were followed for the first pneumothorax attack. 25% of these patients died (p<0.001). In 12 patients monitored after the first attack, complications (such as bronchopleural fistula, empyema, prolonged air leak, atelectasis, etc.) were observed.

Two of our cases with inoperable lung cancer were diagnosed with a bronchopleural fistula and empyema due to a central tumor. In the patient with a poor general condition, antibiotic therapy was initiated; one patient passed away on the 4th day after chest tube placement, while the other passed away on the 2nd day. One of the three patients followed for empyema (aged 64) refused both medical and surgical treatment and was managed with a Heimlich valve. The other two patients (aged 65 and 82) died due to multi-organ failure. In an 80-year-old patient, pulmonary edema developed, and the patient passed away on the 10th day after chest tube placement. Atelectasis developed in six patients. Three patients, aged 70, 78, and 90, recovered with expansion defects. The three patients (aged 70, 75, and 78) had atelectasis along with prolonged air leakage; these patients passed away due to general condition deterioration and multi-organ failure. Mortality occurred in 9 patients with complications, which was statistically significant (p<0.001).

Among the patients with concurrent pneumonia during follow-up, 13 (21.66%) were found to have died (p<0.001). In the group of patients monitored in the ICU, 15 patients experienced mortality, and a statistically significant relationship was observed between intensive care follow-up and mortality (p<0.001) (Table 5).

Table 3

The number of secondary spontaneous pneumothorax attacks, management of pneumothorax, and clinical outcomes in patients

	Number of pneumothorax attacks				p value
	1	2	3	4 or more attacks	
O_2 therapy	5 %8.33	1 %1.66	0	0	0.721
Tube thoracostomy	45 %75	4 %6.66	3 %5	3 %5	0.697
Surgical intervention performed	1 %1.66	0	0	0	0.973
Hemlich Valf	1 %1.66	0	1 %1.66	1 %1.66	0.026
Pleurodesis	6 %10	1 %1.66	3 %5	2 %3.33	0.001
Follow-up in the ICU	28 %46.66	2 %3.33	0	1 %1.66	0.237
Complications	12 %20	2 %3.33	0	0	0.689
Pneumonia	18 %30	2 %3.33	0	1 %1.66	0.862

Table 4

Follow-up Duration Data of Patients with Chest Tube Placement

Variable	Duration (Median[Q1-Q3])	p value
Duration of chest tube placement (n=55)	9.65 [5, 12]	0.025
Total hospitalization duration	17.83 [6, 20]	0.471
ICU stay duration (n=31)	8.58 [4, 12]	0.819

** Values are summarized as Mean ± Standard Deviation or Median [First quartile(Q1), Third quartile(Q3)] depending on the underlying distribution of the variables.*

Table 5

Management of pneumothorax and clinical outcomes in patients

	Mortality	p
Complications (n=14)	9 % 15	<0.001
Pneumonia (n=21)	13 % 21.66	<0.001
Follow-up in the ICU (n=31)	15 % 25	<0.001
	Mean±SD	p
Chest drain duration (n=55)	7.625 ± 5.05	0.542
ICU follow-up duration (n=31)	23± 11.156	0.010

* *ICU: Intensive care unit*

4. Discussion

In this study, we examined cases of SSP in patients aged 60 and above. The prevalence in males in the literature ranges from 61% to 91%.[13,14] Consistent with the literature, our study showed a higher number of male patients, with 51 (85%) males. COPD has been identified as the most common cause of SSP development.[4,15] In the 31 (51.66%) patients who were followed up, underlying lung diseases were detected, and it was observed that the number of cases was higher in males.

In the BTS guidelines, in cases where there is no hemodynamic instability in the clinic, if the pneumothorax is smaller than 1 cm at the hilum level, conservative treatment with bed rest is recommended.[9] In a case with minimal pneumothorax, six patients were followed with conservative treatment. During the observation

period, one patient required a tube thoracostomy.

In the studies by Schoenenberger et al. it was reported that surgery was required in 34% of cases of secondary spontaneous pneumothorax (SSP) due to prolonged air leaks [16]. In elderly patients, due to the presence of severe systemic diseases and underlying pulmonary conditions, pleurodesis is recommended over surgery to prevent recurrence.[10] In cases where air leakage from the chest tube persists for more than seven days, we recommend surgical intervention due to prolonged air leakage. In our study, one patient underwent surgical intervention. The patient accepted surgery on the 12th day and was discharged on the 6th postoperative day. In our series, tube thoracostomy and closed underwater drainage systems were applied to 55 patients (91.66%), with three of them being followed with a Heimlich valve. Pleurodesis was performed in 12 patients (20% of the cases). The study shows that in cases where pleurodesis was applied, the recurrence and mortality rates were statistically significantly lower. It has been reported in the literature that the recurrence rate following the first episode varies between 16% and 52%.[17] In our series, pneumothorax recurrence was observed in 12 cases (9%).

Among these mechanisms are the increase in distal air trapping due to airway obstruction caused by the tumor, the development of pulmonary infarction resulting from tumor embolism, and the formation of a broncho-pleural fistula due to subpleural metastasis.[18, 19] Two of our patients with inoperable lung cancer had a concomitant bronchopleural fistula and empyema. During their follow-up, one patient passed away on the 4th day, and the other on the 2nd day.

In the cases followed, among 26 patients with underlying lung disease and a diagnosis of lung cancer, bullous structures were observed in seven patients with extrathoracic cancer. Mortality was detected in 6.66% of patients with bullous structures.

Surgical indications include recurrent pneumothorax, extensive bullous lung disease, prolonged air leakage, and lung expansion defect.[9,20] In SSP, surgical intervention was considered for patients who did not show expansion after a certain period, before complications developed. Due to the presence of comorbidities, low performance scores, intubation during follow-up, and the development of multi-organ failure, these patients were considered high-risk for surgical intervention. It has been statistically shown that the mortality rate is significantly higher in cases that develop complications and are followed in the intensive care unit.

Studies have demonstrated that the incidence of pneumonia in patients at the time of admission and during follow-up can rise to 11%.[21-24] In our study, 35% of patients were followed up with pneumonia. Pneumonia was present in 21.66% of the deceased patients. A statistically significant relationship was found between pneumonia and mortality ($p<0.001$).

5. Conclusion

Underlying lung disease, concomitant comorbidities, and the development of complications can complicate the management of SSP in elderly patients. The primary goal of the treatment approach is to reduce the recurrence rate and limit mortality by preventing complications. SSP is a recurrent condition, and predicting recurrence in advance is challenging.

In our study, when evaluating the clinical course of elderly patients with SSP, the presence of bullous structures in imaging emerged as a significant risk factor, even in the absence of a diagnosed underlying pulmonary disease. In our study, the development of pneumonia, the need for intensive care unit admission, and the occurrence of complications during follow-up were found to be associated with mortality. These findings are important for determining prognosis. It is anticipated that these data will help us identify goals that can improve survival and quality of life.

This study was conducted at a single center, which limits its generalizability. There is a need for more extensive, multicenter studies.

Statement of ethics

Ethical approval was obtained from the Kayseri City Hospital Clinical Research Ethics Committee. (Date:2024/No:144).

Conflict of interest statement

The author 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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Investigation of IL-6 Expression in Placentas with Term and Preterm Premature Membrane Rupture

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Abstract

Aim: This study investigated IL-6 expression in placentas of patients diagnosed with preterm and term premature rupture of membranes (PROM) via immunohistochemical and in silico analysis.

Methods: Placentas of 40 healthy patients and 40 preterm and 40 term patients diagnosed with term PROM who gave birth in Gynecology and Obstetrics Clinic of Dicle University were subjected to histological tissue embedding protocol. IL-6 immunostaining was performed on tissues. Bioinformatic analysis was performed to explore the potential molecular mechanisms underlying role of IL-6 role in PROM.

Results: IL-6 expression was generally negative in the control group. However, it was significantly higher in both preterm and term PROM groups, with no significant difference between them. In preterm PROM group, IL-6 was recorded as positive in areas with cytotrophoblast, syncytiotrophoblast and fibrinoid accumulation, but was negative in villus connective tissue cells and vascular endothelium. In term PROM group, intense IL-6 expression was observed in trophoblastic layer, syncytial nodes and fibrinoid accumulation, but was generally negative in villous stromal and vascular endothelial cells. Enrichment analysis of IL-6-associated potential PROM targets revealed significant pathways related to microbial responses such as cellular response to lipopolysaccharide, molecule of bacterial origin and biotic stimuli, indicating that IL-6 may modulate PROM predominantly through these pathways.

Conclusions: Compared to control group, significant histopathological changes and increased IL-6 expression were observed in preterm PROM and term PROM groups, with in-silico analysis, indicating PROM increased placental inflammation and damage via IL-6.

Keywords: *Premature rupture of membrane; term; preterm; histopathology; IL-6*

1. Introduction

Amniotic fluid leakage from a defect in the amniochorionic membrane before the onset of labor at any gestational week is called premature rupture of membranes (PROM).[1] This condition is seen in 10% of all pregnancies.[2] If membrane rupture occurs before term (37th week), it is called preterm PROM and is seen in 1-2% of pregnancies. Preterm PROM is known to be the cause of more than one-third of premature births.[3,4] The latent period is the period between membrane rupture and the onset of labor. The term prolonged latent period is used when the duration of membrane rupture exceeds 24 hours. Labor begins within the following 24 hours in 85% of premature membrane ruptures at term.[3,5] Fetal membranes, amnion and chorion, are important structures that provide protection and nutrition for the embryo during pregnancy. While amnion is thin and located inside, chorion is the thick and outer layer. There is a collagen-rich connective tissue between these two layers.[6] Cells in these membranes increase with mitotic growth until the first 28 weeks of pregnancy, but they begin to regress after this process. Although amnion has more tensile strength than chorion, these membranes weaken due to biochemical and biophysical changes as pregnancy progresses.[7] One of the main reasons for this weakening is the decrease in the amount of collagen and the change in its composition.[8] These changes are the basic mechanism that leads to rupture of membranes. Towards term, i.e. when the full term of pregnancy is completed, the most common cause of rupture is physiological changes related to uterine contractions. This situation can usually be called the unnoticed

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onset of labor.[9] Intrauterine infection is an important factor in preterm (early) membrane rupture. However, in many cases, the exact cause cannot be determined.[10]

Cytokines are polypeptide molecules produced and secreted by various cells, especially immune system cells. They play important roles in many biological processes such as inflammation, cell growth, tissue healing, and the body's systemic responses to injuries [11]. Although they have hormone-like properties, they differ from hormones in some important ways.[12] In addition, recent studies have indicated that proinflammatory cytokines such as interleukin play a role in the pathogenesis of genital tract infection and inflammation in preterm labor. In light of this information, we planned to investigate the distribution of IL-6 in normal healthy placentas with premature membrane rupture.[13] In addition to IL-6, other pro-inflammatory cytokines such as TNF-α and IL-8 have also been implicated in PROM pathophysiology. TNF-α has been shown to weaken fetal membranes by inducing matrix metalloproteinase (MMP) activation, while IL-8 contributes to neutrophil recruitment and inflammatory responses in PROM cases.[14,15]

The aim of this study was to determine immunohistochemically the expression of IL-6 in term and preterm placentas with premature membrane rupture in humans and to reveal the possible role and functional relationships of this protein in these placentas.

2. Materials and Methods

2.1. A Placenta Collection

This study was conducted with the approval of the Ethics Committee of Dicle University Faculty of Medicine (date 20.12.2023 and number 2023/7). In the study, pregnant women aged between 18-49 years and without any systemic disease or secondary disease were examined at the Gynecology and Obstetrics Clinic of Dicle University Faculty of Medicine. The patient groups consisted of 40 term pregnant women who gave birth in hospital with the diagnosis of premature membrane rupture and 40 preterm pregnant women. The control group consisted of 40 pregnant women who gave birth in hospital with the diagnosis of healthy pregnancy. Placental tissue samples were taken from all three groups. The patients whose placental tissues would be collected after delivery were informed about the study and their informed consent was obtained. To minimize confounding factors, patients with systemic infections, chronic inflammatory diseases, autoimmune disorders, or maternal diabetes were excluded from the study.[16]

2.2. Placenta Tissue Preparation

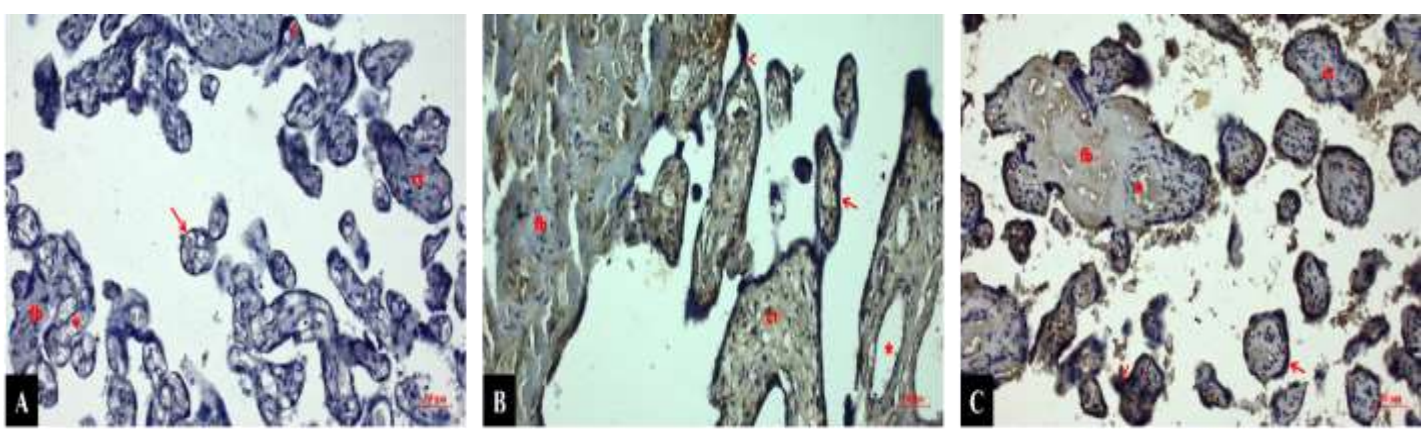
Placenta tissues taken from the maternity clinic after delivery were reduced in size in a manner suitable for histological follow-up. Placenta tissues were first kept in formalin solution for one day. Then, they were kept in running water overnight. Placenta tissues were passed through an ascending ethanol series (50%, 70%, 80%, 90%, 96% and absolute ethyl alcohol) to remove water from the tissues. Tissues were kept in xylene solution 3 times for 30 minutes to remove alcohol. Then, tissues were taken in molten paraffin liquid at 58°C. In the final stage, tissues were embedded in paraffin blocks and 4-6 µm thick sections were taken with a microtome (catalog no: Leica RM2265, Wetzlar, Germany) .

2.3. Hematoxylin-Eosin staining

Sections obtained from paraffin blocks of placental tissues were placed in a bain-marie set at 50°C. Sections were left in a 60°C oven overnight to allow the tissues on the sections to stick to the slide and to melt excess paraffin. Sections were removed from the oven, left at room temperature and allowed to cool. To remove paraffin residues from the sections, sections were kept in renewed xylene solutions for 15 minutes three times. After excess paraffin melted, sections were kept in a decreasing ethanol series (100%, 96%, 90%, 70%, 50% ethyl alcohol) for 10 minutes and excess alcohol was cleaned in distilled water. Harris hematoxylin stain was first applied to the sections for 8 minutes. Sections were kept under tap water for 5 minutes to clean excess staining. Then, the cleaned sections were kept in alcoholic (5%) eosin for 6 minutes. After the staining stage was completed, the sections were quickly dipped in a rapidly rising ethanol series. In order for the tissue in the sections to appear clear and clean, the sections were kept in xylene solutions for 3x15 minutes. Covering medium was added to the sections, they were covered with a slide and stored for examination.

Figure 1

Placental section of the control group. A) In the control group, chorionic villi maintained structural integrity, with minimal fibrinoid accumulation, Cytotrophoblast and syncytiotrophoblast layers appeared intact with negative Il-6expression; B) Preterm PROM group. Increased IL-6 expression compared to control group; C) Term PROM group. Increased IL-6 expression compared to control group. Arrow: Trophoblastic layer, arrowhead: syncytial knot, ct: connective tissue, fb: fibrinoid accumulation, *: vessels. IL-6 immunostaining, Bar: 50 µm, Magnification: 20X



2.4. Immunohistochemical Staining

Sections were washed in phosphate buffer solution (PBS) for 3x5 minutes. After epitope retrieval in ethyl diamine tetraacetic acid (EDTA) solution (pH: 8.0, catalogue no: ab93680, Abcam, Cambridge, USA), sections were treated with hydrogen peroxide solution (catalogue no: TA-015-HP, ThermoFischer, Fremont, CA, USA) for 20 minutes. Nonspecific staining was blocked with blocking solution (catalog no: TA-015-UB, ThermoFischer, Fremont, CA, USA) Primary antibody IL-6 (catalog no: sc-32296, Santa Cruz Biotechnology, Heidelberg, Germany, dilution ratio: 1/100) was dipped onto the tissues and left overnight at +4°C. following biotinylated secondary antibody (catalog no: TP-015-BN, ThermoFischer, Fremont, CA, USA), biotin-streptavidin complex was formed (catalog no: TS-015-HR, ThermoFischer, Fremont, CA, USA). Diaminobenzidine (DAB) (catalog no: TA-001-HCX, ThermoFischer, Fremont, CA, USA) was used as a chromogen. Gill III hematoxylin staining was used as a counter stain. Sections were quickly passed through an increasing ethanol series, cleared in xylene and mounted analyze and visualize with a Zeiss Imager A2 light microscope [17].

2.5. Image J Analysis

IL-6 staining intensity was measured with Image J software (version 1.53, http://imagej.nih.gov/ij). Quantification was recorded by analyzing ten fields from each preparation per group. In the samples, brown color represented positive expression of IL-6 antibody, while blue color represented negative expression of IL-6 antibody. The signal intensity (expression) from an area was calculated by dividing the intensity of IL-6 antibody by the entire area in the sample. The staining area/entire area value was calculated for each sample from ten fields. The median value was measured for the groups and analyzed for semi-quantitative immunohistochemistry scoring. Sections were imaged with a Zeiss Imager A2 light microscope. All images were processed and measured using ImageJ software [18]. For standardization, ImageJ was calibrated using predefined thresholds for brown (IL-6 positive) and blue (IL-6 negative) staining. The software was adjusted to eliminate background noise and ensure consistent measurement across all samples [19].

2.6. Bioinformatics Analysis of IL-6 and PROM Targets

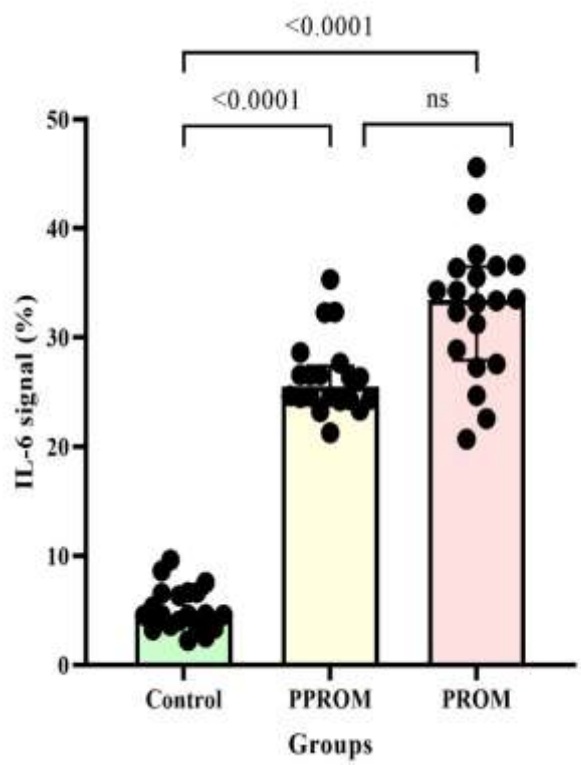
Based on the observed increase in IL-6 expression in both PROM groups, potential IL-6-associated pathways that may play a role in PROM were analyzed from a general perspective using in silico approaches. To elucidate the molecular targets associated with IL-6 in the context of PROM, we analyzed the common targets between IL-6 and the top 20 proteins potentially linked to PROM, as identified in a comprehensive proteome study [20]. The study highlighted these proteins, which exhibited significant fold changes and may be associated with PROM. These proteins are as follows: cysteine and glycine-rich protein 1 (CSRP1), hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD), pyruvate kinase M1/2 (PKM), long-chain-fatty-acid-CoA ligase 3 (ACSL3), fibulin 2 (FBLN2), high mobility group nucleosome binding domain 2 (HMGN2), HMGN3, monocyte differentiation antigen CD14 (CD14), ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2 (BST1), scavenger receptor cysteine-rich type 1 protein M130 (CD163), lamin B1 (LMNB1), intercellular adhesion molecule 1 (ICAM1), protein tyrosine phosphatase receptor type C (PTPRC), cytochrome b-245 heavy chain (CYBB), protein S100-A9 (S100A9), Myeloperoxidase (MPO), cathepsin G (CTSG), Neutrophil elastase (ELANE), integrin subunit alpha M (ITGAM), and matrix metallopeptidase 9 (MMP9). Using Cytoscape software, a protein-protein interaction (PPI) network was constructed involving these proteins and the targets of IL-6, including 100 additional interactions (Confidence: 0.4). Subsequently, pathway intersection analysis was performed to identify potential PROM targets associated with IL-6. Finally, to investigate the role of these shared targets in molecular processes related to PROM, Gene Ontology (GO) biological process (BP) analysis was performed using ShinyGO (version 0.77, http://bioinformatics.sdstate.edu/go77/) [21]. In this platform, enrichments with an FDR value less than 0.05 were considered significant, and the top 10 Gene Ontology Biological Process (GO BP) terms were obtained based on fold enrichment [22].

2.7. Statistical Analysis

The statistical analysis of our study was performed using IBM SPSS 25.0 software (IBM, Armonk, New York, USA). Statistical data distribution in groups was evaluated with the Shapiro-Wilk test. Since the data did not conform to normal distribution, the data were presented as median (Q1-Q3). Comparisons of more than two groups were made with the Kruskal Wallis test, and pairwise group comparisons were made with the nonparametric Dunn's test. Significance was considered for p values <0.05.

Figure 2

Graphical illustration of binary comparisons of IL-6 expression between groups (Dunn's test)



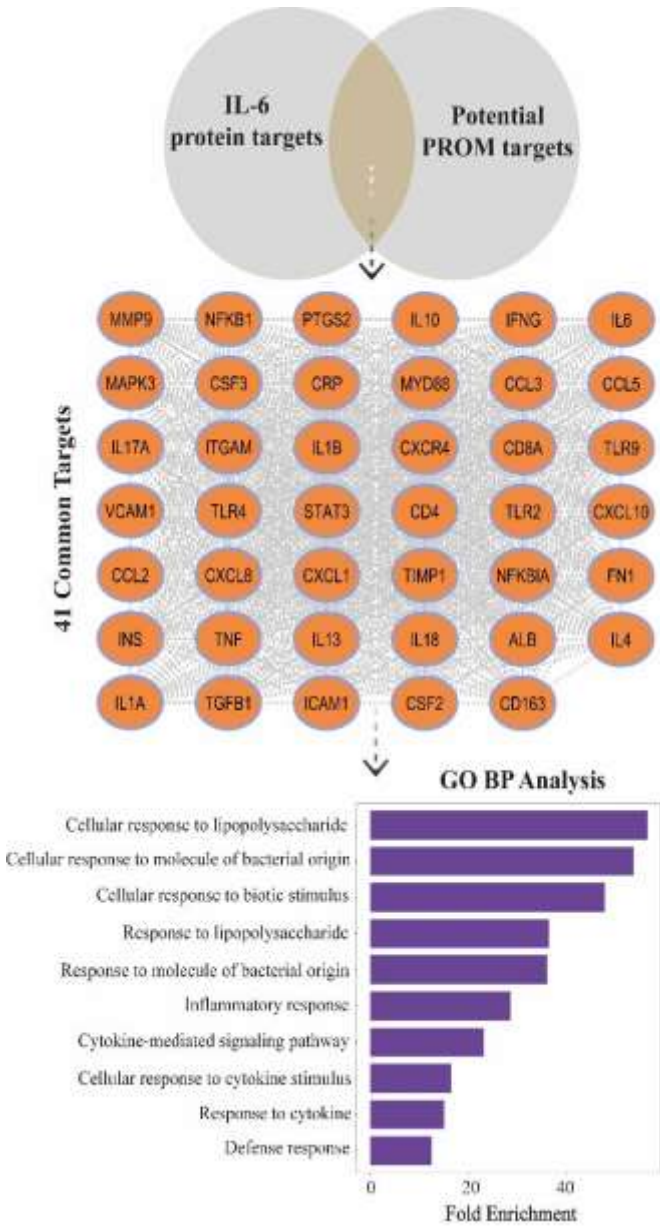
3. Results

3.1. IL-6 expression was upregulated in PROM and PPROM

Figure 1 shows IL-6 immune staining of placental sections per group. In control group, placental components were generally negative for IL-6 expression. IL-6 immune activity was not observed in the trophoblastic layer, syncytial nodes, villous stroma, vascular endothelial cells and fibronid accumulation (Figure 1A). In preterm PROM group, an increase in IL-6 expression was observed in placental tissue. IL-6 expression was recorded as positive in cytotrophoblast and syncytiotrophoblast cells, connective tissue of cells and in areas with fibrinoid accumulation. IL-6 expression was generally negative in vascular endothelium (Figure 1B). Intense IL-6 expression was generally observed in the placental components.

Figure 3

The shared protein targets of IL-6 and premature rupture of membranes (PROM) and their Gene Ontology (GO) Biological Process (BP) analysis.



TLR9: Toll-like receptor 9, ITGAM: Integrin subunit alpha M, FN1: Fibronectin 1, MAPK3: Mitogen-activated protein kinase 3, CXCR4: C-X-C chemokine receptor type 4, VCAM1: Vascular cell adhesion molecule 1, ALB: Albumin, NFKBIA: Nuclear factor kappa B inhibitor alpha, CD8A: CD8 alpha chain, INS: Insulin, TIMP1: Tissue inhibitor of metalloproteinases 1, TLR2: Toll-like receptor 2, ICAM1: Intercellular adhesion molecule 1, MYD88: Myeloid differentiation primary response 88, CCL5: C-C motif chemokine ligand 5, IL13: Interleukin 13, MMP9: Matrix metallopeptidase 9, CXCL10: C-X-C motif chemokine ligand 10, TGFB1: Transforming growth factor beta 1, PTGS2: Prostaglandin-endoperoxide synthase 2, CCL3: C-C motif chemokine ligand 3, CD163: CD163 molecule, CD4: CD4 molecule, CRP: C-reactive protein, IL18: Interleukin 18, TLR4: Toll-like receptor 4, CSF2: Colony stimulating factor 2, IL17A: Interleukin 17A, CXCL1: C-X-C motif chemokine ligand 1, IFNG: Interferon gamma, STAT3: Signal transducer and activator of transcription 3, CCL2: C-C motif chemokine ligand 2, IL4: Interleukin 4, CSF3: Colony stimulating factor 3, IL1A: Interleukin 1 alpha, CXCL8: C-X-C motif chemokine ligand 8, TNF: Tumor necrosis factor, NFKB1: Nuclear factor kappa B subunit 1, IL1B: Interleukin 1 beta, IL10: Interleukin 10, IL-6: Interleukin-6.

Intense IL-6 immune activity was observed in the trophoblastic layer (cytotrophoblast and syncytiotrophoblast), syncytial knotes and fibronid accumulation. Generally negative IL-6 expression was observed in villous stromal cells and vascular endothelial cells. Intense IL-6 expression was also observed in the immune cells of the intervillous area (Figure 1C)

3.2. PROM and PPROM showed significant increase in IL-6 expression

Semi-quantitative measurement of IL-6 immunostaining was shown in Table 1. There was a statistically significant higher IL-6 expressions in both preterm PROM and term PROM groups compared to the control group (p<0.0001).

Binary comparisons between groups were shown in Figure 2. There was no significant IL-6 expression change between PROM and PPROM groups. Both groups showed statistical differences compared to control group (p<0.0001).

Table 1

IL-6 signal intensity in groups

Signal	Control	PPROM	PROM	p value
IL-6 (Median, Q1-Q3)	4.6 (3.7-6.6)	24 (23-27)	33 (28-36)	<0.0001*

** Kruskal Wallis, PROM: Premature rupture of membrane*

3.3. PROM and IL-6 shared biological Process and targets

In the PPI networks associated with IL-6 and PROM, 41 shared proteins were identified. Gene Ontology Biological Process (GO BP) analysis of these proteins revealed several significant GO BP terms, as shown in Figure 3. These terms include: cellular response to lipopolysaccharide, cellular response to molecules of bacterial origin, cellular response to biotic stimulus, response to lipopolysaccharide, response to molecules of bacterial origin, inflammatory response, cytokine-mediated signaling pathway, cellular response to cytokine stimulus, response to cytokine, and defense response. These results indicate that IL-6 is involved in PROM by influencing cellular responses to microbial components, such as lipopolysaccharides and other bacterial molecules.

4. Discussion

Endometrial PPROM is an important obstetric complication in pregnancy and occurs in approximately 3% of all pregnancies. It is also considered to be the cause of 40% of spontaneous preterm births.[23] Preterm births account for 75% of perinatal mortality and 50% of neonatal deaths. This increases the risk of surviving newborns facing long-term health problems.[24] Therefore, PPROM and preterm births can have serious consequences affecting the health of both the mother and the newborn.[25] These data emphasize the importance of the management of PPROM and preterm births. In particular, awareness of risk factors, early diagnosis and development of treatment strategies play a critical role in reducing the negative effects of these complications. There is no definitive method for the detection of PPROM.[6,26] According to our hematoxylin-eosin findings, the placenta in the control group appears to have normal development and healthy function. The presence of fewer syncytial knots and low fibrinoid accumulation indicates that the placenta is healthy. Pathological changes observed in the placentas in the PPROM and PROM groups indicate that the

normal placental structure is disrupted. Degeneration in the chorionic villi, vascular dilatation and congestion, and hemorrhage indicate that the normal physiology of the placenta is disrupted and that there is no suitable environment for fetal development. Edema in the syncytial knots and increased fibrinoid accumulation reflect signs of tissue damage and inflammation in the placenta. Cells with a pyknotic appearance and immune cells in the interstitial area are evidence that the placenta is under inflammation and cellular stress.

Since the correct diagnosis and appropriate management of PPROM are important, various tests and methods continue to be developed.[26,27] Research on biomolecular markers is of great importance to understand the pathophysiology of PPROM, to predict this condition and to develop more effective diagnostic methods.[26] Amniochorionic membranes play an important role as the site of production of inflammatory cytokines, and these cytokines can act as inflammatory mediators leading to systemic and local changes at the fetomaternal interface.[28] Interestingly, in cases of intrauterine infection, these cytokines produced in the uterine cavity first induce a local inflammatory response. The cytokines then pass into the maternal circulation and reach the liver, inducing the release of C-reactive protein (CRP) from hepatocytes and the production of leukocytes from the bone marrow. The increase in cytokines occurs earlier than the increase in CRP and total leukocyte count.[29] IL-6 is a particularly well-known marker of infection and inflammation. IL-6 levels have been found to be significantly elevated in maternal serum, amniotic fluid and vaginal secretions of patients diagnosed with PPROM.[30] Measurement of IL-6 in maternal serum may be useful in detecting asymptomatic intrauterine infections in patients with PPROM, as it is a simpler and less invasive method.[31] A study conducted in South Nigeria showed that IL-6 concentrations in maternal serum were increased in PPROM cases compared to control cases.[32] These findings indicate that IL-6 measurement can be used as a potential early infection marker in PPROM. For these reasons, measurement of IL-6 in maternal serum is important in the early diagnosis of intrauterine infections associated with PPROM and its use in the clinic can be evaluated.[33] In our study, we examined whether IL-6 protein expression in placental tissue samples between the PPROM and control groups and whether IL-6 expression has an effect on the early diagnosis of PPROM.

In examining the underlying mechanisms of the increased IL-6 expression observed in both preterm and term PROM, our in silico analysis revealed that IL-6 significantly contributes to PROM by predominantly modulating microbial response pathways, which are consistently supported by existing literature.[34,35] For instance, IL-6's crucial role in mediating inflammatory responses to bacterial infections has been emphasized, as well as its contribution to initiating the acute-phase response in humans during such infections.[21,36] On the other hand, intraamniotic infection has been frequently correlated with PROM.[37] Consistent with our findings, it has been shown that microbial presence in the amniotic cavity contributes to increased IL-6 levels, and that IL-6, along with MMP9 and CRP, may play a key role in diagnosing intra-amniotic infections in women with PROM.[38] Although studies have reported elevated IL-6 levels in maternal serum and amniotic fluid of PROM patients, the exact mechanisms by which IL-6 contributes to PROM remain to be elucidated.[39] One study demonstrated that during inflammation, the release of IL-6 and tumor necrosis factor-alpha (TNF-α) modulates ADAMTS9, a thrombospondin motif-containing protein, which may contribute to the development of PROM.[40] These findings, combined with our bioinformatic analysis, provide valuable insights into the role of IL-6 in PROM pathogenesis, highlighting its potential as a target for future therapeutic interventions aimed at mitigating inflammation and microbial-induced membrane rupture in both preterm and term cases.

Given its strong association with inflammatory pathways, IL-6 has been proposed as a potential biomarker for PROM detection. Studies have shown that elevated IL-6 levels in maternal serum and amniotic fluid correlate with intra-amniotic infection, which is a major contributor to PROM.[41,42] Serum IL-6 measurement could serve as a minimally invasive tool for early detection and risk stratification in PROM cases, aiding in clinical decision-making

4.1. Limitations and Future Perspectives

This study provides valuable insights into IL-6 expression in term and preterm PROM; however, some limitations should be considered. The relatively small sample size may limit the generalizability of the findings, and maternal factors such as infections or systemic inflammation were not extensively analyzed. Additionally, this study focuses solely on IL-6, while other pro-inflammatory cytokines may also play significant roles in PROM pathophysiology. Future studies should include larger cohorts, consider additional biomarkers, and incorporate longitudinal data to better understand the dynamic changes in IL-6 expression throughout pregnancy.

5. Conclusion

According to our hematoxylin-eosin findings, it was determined that the placentas in the control group continued their normal development and showed healthy function. In contrast, the pathological changes observed in the placentas in the PROM and preterm PROM groups reveal that the normal placental structure was disrupted and created an unfavorable environment for fetal development. Our results emphasize the importance of the inflammatory response of the placenta in cases of premature membrane rupture and preterm birth and help us better understand the potential negative effects of these conditions on fetal development.

Our in silico analysis further supports the hypothesis that IL-6 contributes to PROM by modulating key microbial response pathways, offering a molecular framework for understanding its role in PROM pathogenesis and identifying potential targets for therapeutic intervention.

Statement of ethics

This study was conducted with the approval of the Ethics Committee of Dicle University Faculty of Medicine (date 20.12.2023 and number 2023/7).

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This study was the master thesis of Seval Özmen Ülük, Department of Histology and Embryology, Dicle University.

Author contributions

Conceptualization, F.A.; Data curation, S. Ö. Ü. and F.A.; Investigation, S.Ö. Ü. and F.A.; Methodology, F.A. and T.K.; Project administration, F.A.; Resources, F.A., A.A., F.Ş., Z.Ç. and E.A.; Software, F.A. and T.K.; Supervision, S.E. and H.A.; Validation, T.K., A.A., F.Ş. and Z.Ç.; Writing – original draft, S.Ö.Ü, F.A., T.K., A.A, F.Ş. and Z.Ç.; Writing – review & editing, F.A. and T.K.

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Comparison of Shear Wave Elastography and Dimercaptosuccinic Acid Findings in the Evaluation of Renal Parenchyma

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Abstract

Aim: Dimercaptosuccinic acid (DMSA) renal cortical scintigraphy is the reference standard for the non-invasive diagnosis of renal scar tissue; however, it involves exposure to low doses of radiation. Shear wave elastography (SWE) has recently emerged as a radiation-free, easily applicable technique to measure renal stiffness in renal scar tissue examination. This study aimed to compare the results of DMSA and SWE tests and evaluate whether SWE could serve as an alternative to DMSA in patients.

Methods: This study included 72 patients who underwent elastography of both kidneys prospectively between January 2017 and May 2024 in patients who underwent DMSA examination for various indications. SWE values and stiffness average, standard deviation (SD), median, interquartile range (IQR), and IQR/median values were recorded. Regions of interest were measured in nine areas, three from each of the upper, middle, and lower poles, and mean values were calculated.

Results: The mean age of the patients was 21.8±12.9 years. Among the patients, 47 (33.1%) had ectopic kidneys, and 48 (33.8%) had horseshoe kidneys. The mean SWE value was 7.06±1.1 kPa, the stiffness average was 8.63±5.2 kPa, the stiffness SD was 5.77±3.5 kPA, the stiffness median was 4.15±2.3 kPa, the stiffness IQR was 1.20±1.0 kPa, and the stiffness IQR/median was 16.9±15.1%. A statistically significant correlation was observed between the SWE value and DMSA results (p=0.002).

Conclusions: The SWE value is successful in evaluating renal parenchyma and shows significant correlation with DMSA results.

Keywords: *Shear wave elastography; DMSA; kidney; chronic kidney disease; ultrasonography*

1. Introduction

Amniotic Kidney disease (KD) is a significant public health concern. Therefore, it is particularly crucial to quantitatively assess the extent of early kidney damage and implement timely interventions.[1] Studies have demonstrated that regardless of the initiating factor or the activated signaling pathway, the main pathophysiological changes in chronic progressive kidney damage are inflammation and fibrosis.[2] Inflammation arises from the infiltration of inflammatory cells triggered by local tissue damage, which exacerbates kidney damage through the release of inflammatory mediators and initiates the repair process. Fibrosis is fundamentally an excessive reparative process that leads to a continuous loss of renal parenchyma and the relentless progression of KD.[3] Thus, in addition to routine biochemical markers, monitoring the degree of renal fibrosis constitutes a critical element in assessing the treatment status of patients with chronic kidney disease (CKD).[3]

The primary nuclear medicine modality employed for assessing renal parenchymal status and determining the level of fibrosis is dimercaptosuccinic acid (DMSA) scintigraphy. However, as a nuclear imaging method, DMSA scintigraphy requires an extended

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patient preparation period and contributes to higher costs, particularly in patient populations requiring follow-up.[4]

Shear wave elastography (SWE) technology is a non-invasive, rapid, straightforward, and objective method for quantitatively assessing tissue stiffness.[5] Today, SWE is widely used in ultrasound imaging and constitutes a substantial portion of the contemporary literature on ultrasonography (USG). SWE has a substantial body of discoveries and experiences related to solid organs such as the liver and pancreas, demonstrating notable progress in its clinical applications. On an international scale, the use of SWE technology for the quantitative assessment of liver fibrosis has gained widespread acceptance. In recent years, numerous studies have also been conducted on the application of SWE in evaluating renal fibrosis.[5]

In this study, our objective was to evaluate whether SWE parameters, including elasticity value, stiffness average (avg), and interquartile range (IQR), correlated with DMSA findings in patients undergoing DMSA examination due to the risk of KD.

2. Materials and Methods

2.1. Patient selection and study design

The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee of Adana City Training and Research Hospital on November 4, 2024 (number: 2024/3145). Since the study was retrospective, the requirement for informed consent was waived. Following ethics committee approval, additional authors were included in the study to review the clinical information of patients, ensuring that the four radiologists remained blinded to the patient data.

For this study, patients who underwent DMSA scintigraphy between January 2017 and May 2024 were identified and subsequently underwent renal USG and shear wave USG. Patients were excluded from the study if they exhibited renal atrophy (n = 29), grade 2 or higher echogenicity increase on grayscale USG (as renal parenchymal boundaries may be compromised) (n = 32), hydronephrosis (n = 14), renal parenchymal thickness under 1 cm (due to the region of interest [ROI] size being set at 1 cm) (n = 37), inadequate respiratory cooperation during shear wave USG (n = 18), or obesity with a skin thickness exceeding 10 cm (n = 24). A total of 72 patients were included in the study. The difference in DMSA (%) values between the two kidneys of each patient was calculated, and the correlation between these differences and the SWE parameters of the affected kidney was analyzed.

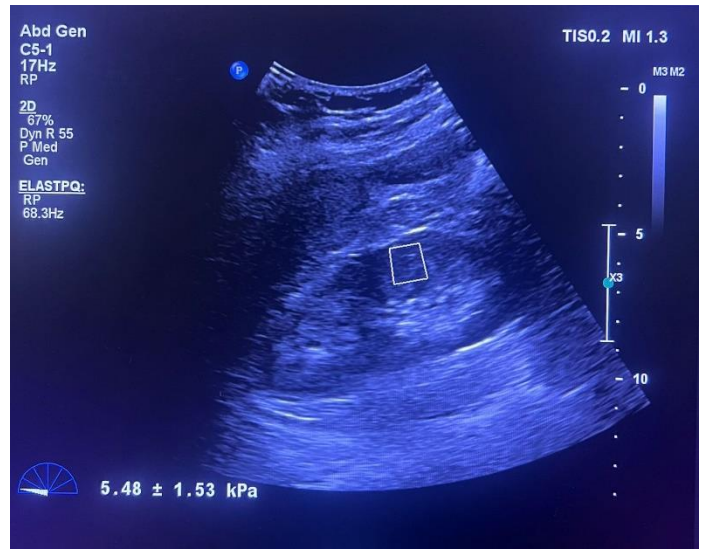
2.2. Renal Ultrasonography

In this study, renal USG was performed using a high-resolution USG device (Philips EPIQ 7) with a 1–5 MHz high-resolution convex probe (Philips Health Care, Bothell, WA, USA). All USG images were obtained after at least six hours of fasting and 20 minutes of rest. Initial images were acquired using grayscale B-mode USG, followed by the acquisition of quantitative shear wave parameters.

Kidney size, cortical thickness, and parenchymal echogenicity were evaluated using grayscale imaging. Patients with grade 2 or higher echogenicity were excluded from the study. Kidney length was measured from the upper to the lower pole. The distance between the renal hilum and the renal capsule was measured in the coronal plane at the inter-polar level. Cortical thickness was measured between the base of the central medullary pyramid and the renal capsule. Renal USG was performed in the right and left lateral decubitus positions. Minimal compression was applied to the probe, and the patients were asked to hold their breath for a few seconds to minimize kidney movement during respiration (Fig.1).

Figure 1

Shear wave elastography (SWE) measurement



Measurements were taken after placing ROI on targets in grayscale renal USG images. The ROI was vertically placed on a renal cortex area free of vessels or cysts. The primary axis of the ROI was adjusted to be parallel to the axis of the renal pyramid. Measurements were obtained at the shortest possible ROI target distance, with the ROI size fixed at 1 cm. Efforts were made to minimize compression during imaging to avoid mechanical pressure on the kidneys. Both kidneys were imaged using the same technique. For each kidney, nine valid measurements (three each from the upper, middle, and lower poles) were obtained, and the avg value was calculated. The results were expressed in kPa. Conventional, Doppler, and SWE examinations were conducted by two experienced radiologists. The total USG examination time was approximately 25–30 minutes.

2.3. Renal Scintigraphy

A dose of 99mTc-DMSA (185 MBq) was injected intravenously into patients, and static planar views of the kidneys in anterior and posterior projections were acquired after three hours. Renal counts were obtained in a posterior projection using a gamma camera (Optima NM/CT 640, General Electric, USA). Counts in each kidney were normalized for perirenal background reading, tissue absorption, and radionuclide decay. The renal uptake of 99mTc-DMSA was expressed as a percentage of the net injected activity fixed in each kidney, providing a relative functional percentage for each kidney. Kidneys with higher percentages of 99mTc-DMSA uptake were considered dominant. The sum of the individual renal function percentages was 100% on both sides.

In transverse sections, the operator identified the slice representing the kidney and outlined a ROI around the organ. For volumetric measurements (in cubic centimeters), the number of pixels above the threshold in all slices was multiplied by the slice thickness. For concentration measurements, the threshold value was subtracted from all pixels in the ROI in all slices. Non-zero pixels with counts above the threshold were used to calculate concentration. Counts per voxel were converted to concentration units (kBq/cm^3) using a regression line obtained from previous phantom measurements. The percentage injected dose per cubic centimeter (%ID/cm^3) was calculated using this corrected value for radioactivity decay (Fig.2). Renal uptake was then determined by multiplying this value by the renal volume (in cubic centimeters).

Figure 2

Total relative Dimercaptosuccinic acid (DMSA) uptake % distribution of both kidneys

Table 1

Distribution of demographic data and DMSA and shear wave elastography values

	Number (n)	Percentage (%)
Sex		
Female	37	51,4
Male	35	48,6
Kidney (right/left)		
Right	39	54.2
Left	33	45.8
Ectopic kidney	7	9.8
Horseshoe kidney	13	18.1
Vesicoureteral reflux	28	38.8
Allogenic graft rejection	24	33.3
	Mean ± SD	Median (Min–Max)
Age	21.8 ± 12.9	17 (2–34)
Right kidney DMSA %	50.7 ± 11.0	52 (11.05–79.2)
Left kidney DMSA %	48.6 ± 12.3	48 (0.33–88.95)
Renal parenchymal thickness (mm)	13.5 ± 2.2	13.3 (10–25)
Renal long axis (mm)	99.3 ± 17.6	95.5 (71–162)
Kidney-skin distance (mm) (average of lower, middle, and upper poles)	45.6 ± 10.3	44 (22–70)
Shear wave elastography value	7.06 ± 1.1	7.14 (3.22–12.1)
Stiffness avg (kPa)	8.63 ± 5.2	7.51 (1.32–45.7)
Stiffness SD (kPa)	5.77 ± 3.5	5.13 (0.34–25.5)
Stiffness median (kPa)	4.15 ± 2.3	3.87 (1.01–18.6)
Stiffness IQR (kPa)	1.20 ± 1.0	0.89 (0.08–6.81)
Stiffness IQR/median (%)	16.9 ± 15.1	12 (1.2–77.9)

DMSA: dimercaptosuccinic acid, avg: average, SD: standard deviation, IQR: interquartile range

2.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Categorical measurements were summarized as counts and percentages, while continuous variables were expressed as means and standard deviations [SDs] (with median and minimum–maximum values where necessary). Cohen's kappa coefficient was used for both intra- and inter-reader assessments. Receiver operating characteristic (ROC) curve analysis was conducted to determine the area under the curve (AUC), sensitivity, and specificity. A significance level of 0.05 was used for all tests. 1.

Table 2

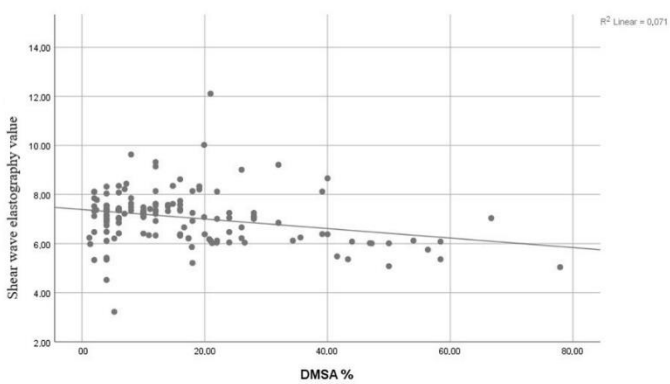
Correlation between changes in DMSA (%) and shear wave elastography parameters

	DMSA % change	
	r	p
Age	0.143	0.090
Renal parenchymal thickness (mm)	-0.101	0.231
Renal long axis (mm)	-0.143	0.089
Kidney-skin distance (mm) (average of lower, middle, and upper poles)	0.084	0.380
Shear wave elastography value	-0.255**	0.002
Stiffness avg (kPa)	0.027	0.746
Stiffness SD (kPa)	-0.132	0.116
Stiffness median (kPa)	-0.027	0.751
Stiffness IQR (kPa)	0.116	0.169
Stiffness IQR/median (%)	0.111	0.187

**p < 0.05, **p < 0.01, Spearman's rho. DMSA: dimercaptosuccinic acid, avg: average, SD: standard deviation, IQR: interquartile range*

Figure 3

Correlation distribution between DMSA and SWE values (DMSA: dimercaptosuccinic acid, SWE: shear wave elastography).



3. Results

Of the patients included in the study, 77 (54.2%) were female. Within the patient group, 47 (33.1%) had ectopic kidneys, and 48 (33.8%) had horseshoe kidneys. The mean age of the patient group was 21.8 ± 12.9 years. The mean renal parenchymal thickness was 13.5 ± 2.2 mm, and the mean kidney length was 99.3 ± 17.6 mm. Among the patients followed up for CKD, 73 had their left kidney and 69 had their right kidney identified as being at risk (Table 1).

No statistically significant relationship was found between DMSA distribution and patient age, renal parenchymal thickness, renal longitudinal axis, or the distance of the kidney from the skin. Similarly, no relationship was observed between DMSA distribution and stiffness values (avg, SD, median, IQR, IQR/median [%]) derived from SWE findings (Table 2).

A significant correlation at a substantial level of agreement was identified between the SWE values and DMSA values (κ = 0.071) (Table 2, Figure 3).

4. Discussion

Despite its association with low-dose radiation exposure, DMSA renal cortical scintigraphy remains the gold standard imaging method for the non-invasive diagnosis of renal scar tissue.[6] Recently, SWE has emerged as a technique for assessing renal stiffness in the evaluation of renal scarring. Renal parenchymal fibrosis is the most significant marker of KD and leads to changes in the mechanical properties of the kidneys, which can be objectively measured with DMSA.[7] DMSA is frequently used in the diagnosis of ectopic kidneys, horseshoe kidneys, and vesicoureteral reflux in pediatric patients, as well as in detecting fibrosis in suspected cases of allogeneic graft rejection.[8] Certain conventional renal ultrasonography findings, such as decreased kidney size, reduced cortical thickness, and increased echogenicity in the cortex, may indicate parenchymal KD.[9] However, by the time these findings are typically observed, fibrosis has progressed, and the patient is often already diagnosed with CKD. Thus, there is a clear need for parameters that can assist in earlier diagnosis.

Given the current popularity of SWE in identifying pancreatic and liver fibrosis, it is not surprising that efforts have been made to investigate its potential in detecting renal fibrosis.[3] The stiffness values obtained from SWE tests have also gained prominence recently. However, SWE has certain limitations, including inconsistent availability in clinical settings and the absence of standardized normal stiffness values for different patient groups.[10] Another primary disadvantage of SWE is the lack of an established cut-off value for fibrosis in solid organs. This limitation is particularly evident in renal assessments, where the inconsistencies and gaps in the literature are pronounced due to the novelty of the method.[11] Renal SWE findings are not routinely documented in conventional ultrasonography results, and stiffness values are only measured in specific diseases or studies.[12] SWE is a cost-effective, reliable, and non-invasive USG technique for determining tissue elasticity.[13,14] However, the current study also found no relationship between DMSA values and stiffness parameters. The success of stiffness parameters in reflecting renal fibrosis remains unclear. There is a need for further studies with larger patient cohorts to clarify this issue.

The study has some limitations. First, the study was conducted at a single center with a relatively small number of patients. Second, other parameters used to evaluate renal function, such as diethylenetriamine pentaacetate and glomerular filtration rate, were not utilized in this study.

5. Conclusion

The correlation between SWE values and DMSA demonstrates its potential role in detecting fibrosis. SWE can be utilized in the follow-up evaluations of patients suspected of having renal fibrosis.

Statement of ethics

The study was conducted in accordance with the tenets of the

Declaration of Helsinki and approved by the Ethics Committee of Adana City Training and Research Hospital on November 4, 2024 (number: 2024/3145).

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None to declare.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The available data are maintained by Adana City Training and Research Hospital and are securely stored within the institution. These data cannot be shared without prior authorization. Researchers who meet the criteria for accessing confidential data are encouraged to contact the Ethics Committee of Adana City Hospital for further assistance. Data Access/Ethics Committee: adanasehir.etikkurul@saglik.gov.tr

Author contributions

Conceptualization, SS, TDA.; Data curation, SS, ZOU, APK.; Investigation, SS, HBO, APK.; Methodology, F.A. and T.K.; Project administration, SS.; Resources, SS, HA, TDA, ZOU, APK, HBO.; Writing – original draft, SS, HA, TDA,.; Writing – review & editing, SS, HA, TDA, ZOU, APK, HBO.

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Comparison of Perioperative Malposition Rates of Fixed and Adjustable Suspensory Button Implants Used for Femoral Fixation During Anterior Cruciate Ligament Reconstruction

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Abstract

Aim: This study compared the malposition rates of fixed and adjustable suspensory button implants used for femoral fixation of the graft during anterior cruciate ligament (ACL) reconstruction and examined the effectiveness of intraoperative imaging in managing these complications.

Methods: This retrospective study evaluated 187 patients who underwent arthroscopic ACL reconstruction. The patients included in the study were categorized into two groups according to the type of femoral suspensory button (FSB) implant used: fixed suspensory button (FxSB) and adjustable suspensory button (ASB). Button malpositions were determined and recorded with intraoperative images in cases where fluoroscopy was used and postoperative X-ray radiographs in cases where fluoroscopy was not used. Malposition rates were compared between the two groups, and risk analysis was performed.

Results: Malposition was observed in 24 patients (12.8%). It occurred in 5 patients (5.6%) in the FxSB group and 19 patients (19.3%) in the ASB group (p=.012). ASB implants were associated with a 3.5-fold higher risk of malposition compared to FxSB implants (OR: 3.57, 95% CI: 1.36–10.1, p=.002).

Conclusions: ASB implants were linked to a significantly higher rate of button malposition than FxSB implants. Intraoperative fluoroscopy proved effective in detecting and correcting malpositions across both implant types.

Keywords: *ACL reconstruction; suspensory button implant; fluoroscopy; malposition*

1. Introduction

The technique of suspensory fixation of anterior cruciate ligament (ACL) grafts has become popular with the advent of femoral suspensory button (FSB) implants. Various problems with the previously widely used screw fixation method have led surgeons to use suspensory fixation techniques increasingly.[1-3] Two types of FSB implants are commonly used today. Fixed suspensory button (FxSB) implants are the first devices to be used. Careful calculation of the tunnel length and the appropriate implant length during surgery is very important for the survival of the reconstruction.[4,5] Adjustable suspensory button (ASB) implants are relatively newer implants and can be used without complex tunnel and implant calculations.[6,7] Many biomechanical studies have shown that FSB implants provide excellent fixation and tension in the graft tendon, as well as ease of use.[8-10] Despite these advantages, perioperative malposition is well-known to orthopedic surgeons. However, there is insufficient information on the malpositioning rates of these devices, and FxSB has only been partially addressed in a few studies.[11,12]

The most commonly reported malposition is due to excessive pulling of the button during removal from the femoral tunnel. This technical error can cause the buttons to dislodge through the iliotibial band, vastus lateralis, and even the skin, resulting in soft tissue interposition between the button and the lateral femoral cortex. If the surgeon does not recognize this condition, the button will rotate outside of the vastus lateralis or iliotibial band and not make cortical contact.[7,13] Without early intervention, ischemic

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necrosis of the intervening tissue may develop, failing to maintain proper graft tension, which is key to the success of ACL reconstruction. O'Brien et al. reported a 15.7% rate of soft tissue interposition in their study of ACL reconstruction using an FSB implant (Arthrex Tightrope RT or Mitek Rigid Loop).[14] Mae et al. (Smith & Nephew EndoButton) found this rate to be 25.2%.[15] Another important fixation failure is intra-tunnel malposition caused by the under-drawing of button implants.[16] In a study by O'Brien et al., intra-tunnel malposition was reported in 9.8% of FSB implants.[14] Suppose such complications are detected by the surgeon intraoperatively. In that case, the necessary intervention can be performed and an optimal button fit can be achieved. However, in cases that are not detected intraoperatively, it can have devastating consequences, leading to a second surgical intervention in the early period or even revision ACL reconstruction in neglected cases. In a recent study on FSB implants, Gürpınar et al. showed that soft tissue interposition of 2 mm or more between the implant and the femoral cortex negatively affects the results after ACL reconstruction.[4]

The purpose of this study was to determine the perioperative malposition rates of FxSB and ASB implants, which are now widely used for femoral fixation of the graft in ACL reconstruction, and to determine the effectiveness of intraoperative imaging in managing these complications.

2. Materials and Methods

This study was conducted after approval by our institutional human research ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and written informed consent was obtained from all subjects. The records of 187 patients (133 males, 54 females; mean age: 29.5 years [SD: 1]) who underwent consecutive arthroscopic ACL reconstruction for ACL tears at two different treatment centers by a single orthopedic surgeon between June 2012 and February 2022 were retrospectively reviewed. The following criteria were sought for patients included in the study: Physical examination and radiographic determination of ACL tear, arthroscopic anatomic single tunnel ACL reconstruction, use of autogenous hamstring tendon grafts, and FSB implants for femoral fixation. Patients with revision ACL reconstruction and multiple ligament injuries were not included in this study. According to the type of FSB implant used, the patients included in the study were divided into two different groups: the FxSB implant group (Tulpar LoopFix Button, DePuy Synthes Rigidloop Endobutton Cortical System) and the ASB implant group (Tulpar LiftFix Button, DePuy Synthes Rigidloop Adjustable Cortical System).

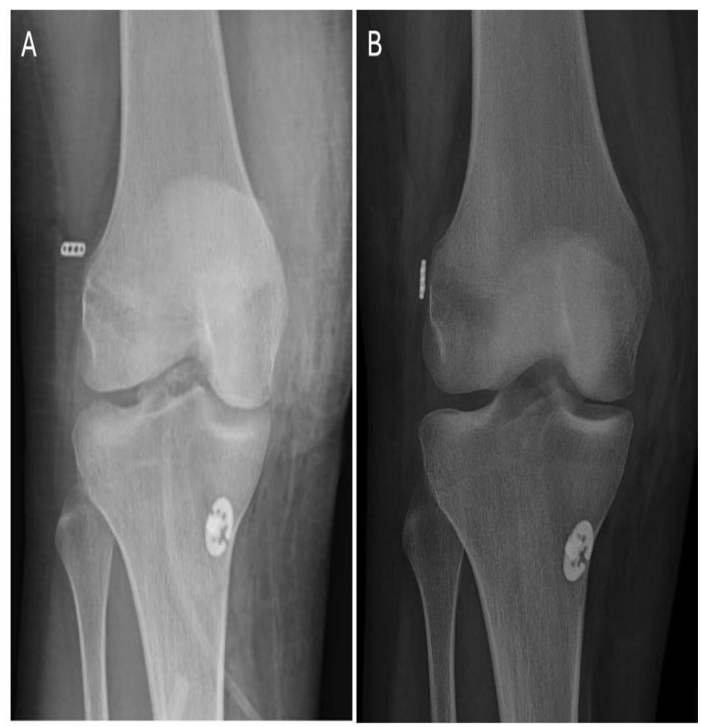
2.1. Surgical technique-Perioperative imaging methods

An autogenous hamstring graft obtained by folding the gracilis and semitendinosus tendons in two was used in all our patients. Our arthroscopic technique used the anatomic single tunnel ACL reconstruction technique described by Kim et al. in 2011.[17] Depending on the type of FSB implant used, tunnel, tendon, and implant preparation were performed according to the manufacturer's instructions. After the graft and associated suspension button were seen in the intercondylar notch, they were pulled toward the lateral femoral cortex, and the surgeon applied force to the graft from the tibial side at the point where it was felt to change as it exited the cortex. With this force, it was understood that the tendon and button implant would not return, and thus, the implant was properly positioned in the femoral cortex. In cases where C-arm fluoroscopy was used, intraoperative images were obtained at this stage, and this recorded data was analyzed. In cases where C-arm fluoroscopy was not used, radiographs obtained at the first postoperative visit were evaluated and analyzed.

Soft tissue and intra-tunnel malpositions were identified and recorded in both groups. Although the definition of soft tissue malposition is not well known, recent studies have defined it as a distance of more than 2 mm between the button and the cortex of the femur and identified it as a critical value in terms of its clinical importance.[4,18] In our study, we defined this as the critical value. In the cases where we used fluoroscopy during surgery, the malpositions were corrected by a 2 cm lateral femoral skin incision, and the optimal fit of the button to the cortex was ensured. For malpositions detected on postoperative imaging without fluoroscopy, no observation was performed in any patient, and a second early surgical procedure was performed to ensure appropriate reconstruction (Figure 1). In our study, these recorded data were analyzed and compared between groups, and risk analyses were performed using subgroup studies.

Figure 1

A: Malposition of the femoral button implant B: Image of the patient with the button implant fixed in the optimal position with a secondary surgery.



2.2. Statistical Analysis

R 4.2.3 and SPSS 22.0 versions were used for statistical analysis. The chi-square test, a non-parametric test, was applied to determine the significance level of the relationship between categorical variables. In accordance with the conditions of the cross-table created for the Chi-Square analyses, the analysis of the difference between the groups was performed using Yates' Correction and Fisher's Exact methods. The results of the tests performed on the variables in the study were evaluated at a 95% confidence interval, and $p<0.05$ was considered significant. Risk analysis was performed using binary logistic regression analysis between the groups in terms of secondary surgery. For statistical significance, $p<0.05$ was accepted, and the data are presented as odds ratio (OR) and 95% confidence interval (CI).

Table 1

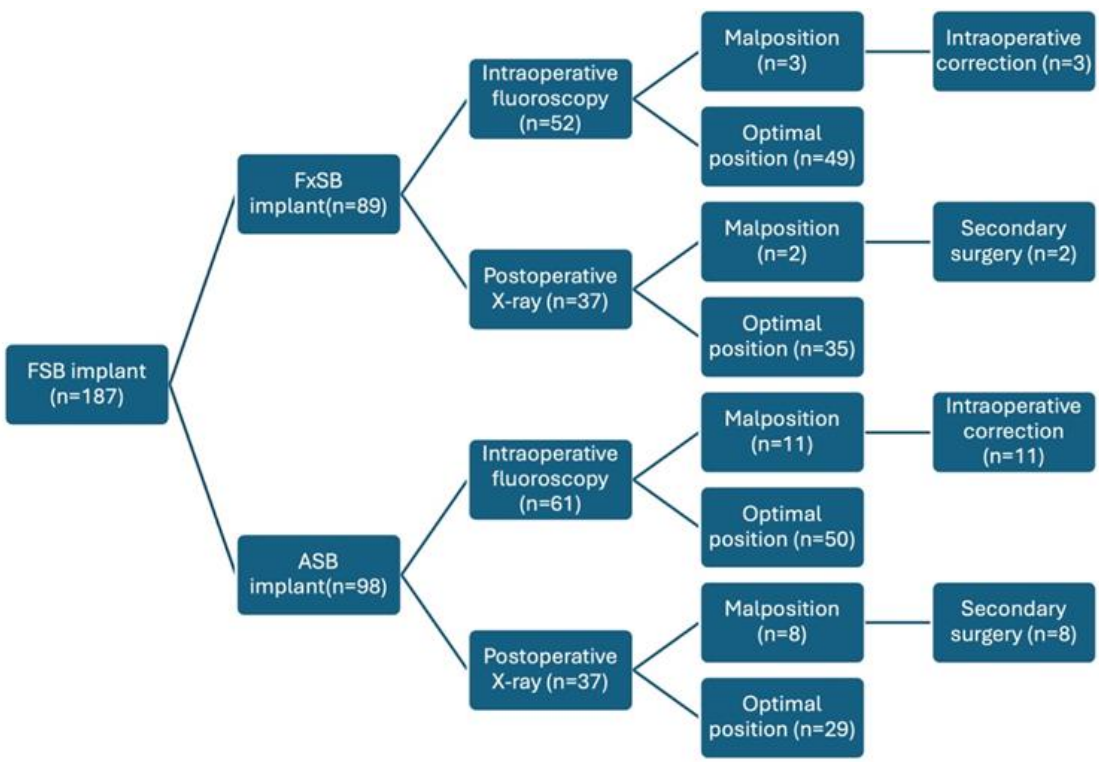
Demographic and imaging characteristics of patients

	FxSB implant (n=89)	ASB Implant (n=98)	P
Sex			
• Male	63(70.8%)	70 (71.4%)	.923
• Female	26 (29.2%)	28 (28.6%)	
Side			
• Right	47	58	.626
• Left	42	40	
Average age	29.2(SD:1)	29.7(SD:1)	.681
Perioperative imaging method			
• Intraoperative fluoroscopy	52(58.4%)	61(62.2%)	.594
• Postoperative X ray	37(41.6%)	37(37.8%)	

Note: FxSB: fixed suspensory button. ASB: adjustable suspensory button.

Figure 2

Malposition results encountered in patients undergoing ACL reconstruction according to the button implant used and perioperative imaging methods.



Note: FxSB: fixed suspensory button. ASB: adjustable suspensory button.

3. Results

In our study, 89 patients (63 males, 26 females; mean age: 29.2 years) received FxSB implants, and 98 patients (70 males, 28 females; mean age: 29.7 years) received ASB implants. The number of patients who underwent intraoperative fluoroscopy was 52 (58.4%) and 61 (62.2%) in the FxSB and ASB implant groups, respectively. Intraoperative fluoroscopy was not used in 37 patients (41.6%) in the FxSB group and 37 patients (37.8%) in the ASB group. X-ray images obtained at the first postoperative visit were utilized. Demographic characteristics and perioperative imaging techniques of the patients according to the groups are presented in Table 1.

When the perioperative images of all patients included in the

study were analyzed, malposition was detected in 24 patients (12.8%) (Figure 2). When the FxSB and ASB implant groups were considered separately, the number and rates of malposition were 5 (5.6%) and 19 (19.3%), respectively. Statistically, the malposition rate was higher in the ASB implant group (p=.0123). In the regression analysis, it was determined that the risk of malposition was 3.5 times higher in the ASB implant group than in the FxSB implant group (OR: 3.57 (p=.0017) 95% CI (1.36-10.1)). When the images were analyzed in detail, it was determined that all five patients in the FxSB implant group developed soft tissue malposition, while 18 patients in the ASB group developed soft tissue malposition, and one patient developed intra-tunnel malposition.

Another important point that we examined in our study was the effect of intraoperative fluoroscopy on the identification of malpositions and subsequent optimal button positioning. Intraoperative fluoroscopy was used in three of 52 patients (5.8%) in the FxSB group and eleven of 61 patients (18%) in the ASB group and was found to be significantly higher in the ASB implant group (p=.003). Regression analysis showed that the risk of malposition was higher in the ASB implant group than in the FxSB implant group (OR: 3.66) (p=.042) 95% CI (1.01-13.4). In all of these patients, optimal positioning of the cortical buttons was achieved with intraoperative interventions without the need for a second surgical intervention. On the other hand, malposition was detected on X-ray images taken during the first visit in two (5.4%) of 37 patients in the FxSB group and in eight (21.6%) of 37 patients in the ASB group (p=.089) and optimal button positioning was achieved in all of these patients with a secondary surgical intervention in the early period. When the results of the risk analysis were analyzed, it was determined that the riskiest group in terms of secondary surgical intervention was the patients with ASB implant and no intraoperative fluoroscopy (OR: 5.4) (p=.041) 95% CI (1.0-24.5).

4. Discussion

In this study, we found that ASB implants resulted in a significantly higher rate of malposition in ACL reconstruction compared to FxSB implants. We also observed that the use of intraoperative fluoroscopy in both implant groups reduced the likelihood of revision surgery. In particular, patients in the ASB group without intraoperative fluoroscopy had the highest rate of secondary surgery. To our knowledge, this is one of the few studies comparing fixed and adjustable suspensory button implants in terms of perioperative fixation failure. Additionally, we believe our evaluation of intraoperative fluoroscopy contributes valuable data to the current literature.

Correct button placement is important with FSB implants because proper graft fixation and implant positioning are critical to maintaining graft tension.[19-21] There is no clear information in the literature regarding misplacement rates of FSB implants. Incorrectly positioned button implants have been shown to cause postoperative pain, button migration, and even revision ACL reconstruction.[8,18,22-24] The study by Simonian et al. is one of the first studies to address button malpositioning and soft tissue interposition with FSB implants.[5] In their cadaveric study, they found that the vastus lateralis and iliotibial band can be positioned between the endobuttons (Acufex Microsurgical Inc, Mansfield, MA) and the femoral cortex, which can lead to ACL reconstruction failure. With the widespread use of FSB implants, case series related to malposition have begun to be reported. The first of these is by Mae et al.[15] They reported that they used the FxSB implant (EndoButtons (Smith & Nephew Endoscopy) in their anatomic double tunnel ACL reconstruction study and found a 25.2% rate of soft tissue malposition. Büyükkuşçu et al. used the FxSB implant (Rigidloop™ cortical fixation system, DePuy Synthes) in their series of anatomic single tunnel ACL reconstruction and reported a malposition rate of 37.6%.[25] In our study, the malposition rate was 5.6% in our group of cases in which we used the FxSB implant. There may be several reasons for this low rate. First, Mae et al. accepted the minimum distance between the femoral cortex and the button implant as 1 mm for malposition and performed a double tunnel ACL reconstruction instead of a single tunnel. Similarly, Büyükkuşçu et al. accepted this distance as 1 mm. Another reason may be the failure to follow the manufacturer's technical recommendations for femoral tunnel preparation, which is especially important when using FxSB implants. Mae et al. stated in their report that they used a different technique for tunnel preparation. Büyükkuşçu et al. did not provide any information about the manufacturer's technique in their report. In our study, femoral tunnel preparation was performed according to the manufacturer's technical recommendations. One of the most recent studies on FxSB implants was performed by Gürpınar et al. (EndoButtons (Smith & Nephew Endoscopy, Andover, MA), and in their study consisting of 156 patients, they characterized soft tissue interposition over 2 mm as malposition and stated that it is clinically associated with poor functional outcome. This rate was reported to be 5.2% in their series and was found to be compatible with the results of our study.[4]

ASB implants are relatively new devices, and there are not enough studies on malposition rates. In a study by Balldin et al. using ASB implants (Arthrex Tightrope RT) and not using fluoroscopy, they found a 10% rate of soft tissue interposition (>2 mm) on postoperative X-ray images but did not mention intra-tunnel malposition.[18] O'Brien et al., using intraoperative fluoroscopy, reported a 25.5% malposition rate, of which 15.7% was soft tissue interposition, and 9.8% was intra-tunnel malposition.[14] In our study, 19.3% malposition was detected in the group in which we used ASB implants, 18.4% of which were soft tissue interposition, and 1% of FxSB had intra-tunnel malposition. None of the previous studies have compared the malposition rates of FxSB and ASB implants. The most important data we obtained in our study is that this rate is related to the type of implant. It is clearly seen that FxSB implants result in much less malposition than ASB implants. We attribute this to the importance of tunnel-implant length matching during femoral tunnel preparation when using FxSB implants. The surgeon has to follow the technical details recommended by the manufacturer to optimize this match, thus reducing the margin of error.[21,26-28] On the contrary, when preparing the femoral tunnel in ASB implants, both the tunnel length and the implant length are completely up to the surgeon's option.[7,29-31] Therefore, we believe that the higher malposition rate observed with ASB implants in our study may be attributed to the greater surgical variability in tunnel and implant length selection. The absence of a standardized matching guide or fixed reference points may increase the margin for error.

Another contribution of our study is the demonstration that the use of intraoperative fluoroscopy is a useful method to prevent possible secondary surgery by intraoperatively identifying inappropriate button positioning in ACL reconstructions using FSB devices. A standardized method for confirming proper button implant positioning has not yet been defined. Some clinicians have emphasized that the use of fluoroscopy may be useful, while others have advocated proper button positioning by direct visualization through an arthroscopic or lateral femoral skin incision. Arthur et al. compared the malposition rates of these three techniques on postoperative radiographs.[32] They reported that no malposition occurred with intraoperative fluoroscopy or open skin incision visualization, whereas direct arthroscopic visualization resulted in a 4.6% malposition rate (p< .05). Each technique has advantages and disad-

vantages. Ensuring proper button positioning with arthroscopic visualization is technically difficult and increases operative time.[13,33-35] Positioning through an open skin incision requires a larger incision and again increases the surgical time.[36,37] Intraoperative fluoroscopy appears to be a useful method of visualizing proper button positioning without the need for an additional incision and without significantly increasing operative time.[18,32] Balldin et al. reported a significant difference in button positioning between the intraoperative fluoroscopy group and the non-intraoperative group and stated that intraoperative fluoroscopy is a reliable method to detect and prevent malpositioning.[18] In our study, 14 malpositions were identified and corrected intraoperatively among 113 patients with fluoroscopy, preventing any need for revision surgery. Conversely, 10 of 74 patients in the non-fluoroscopy group required early reoperation due to unrecognized malposition. The reoperation rate was significantly higher in this group ($p < .05$), supporting the value of fluoroscopy as a preventive tool.

This study has several limitations. First, our ability to provide information, which is typical of a retrospective study, is limited to what is documented in the medical records. Therefore, we could not provide more details about the surgical techniques used, especially in patients who underwent a second surgery. Second, although our sample size seems adequate, it is relatively small. Finally, the experience of orthopedic surgeons may have changed between 2012 and 2022, which may have affected the results. Our study also has some strengths. In particular, the fact that it includes a control group and that a single orthopedic surgeon performed the surgeries is the strongest feature that distinguishes it from other studies. In addition, following the technical recommendations of the implant manufacturers during surgery is another important feature that effectively standardizes the results.

5. Conclusion

ASB implants were linked to a significantly higher rate of button malposition than FxSB implants. Intraoperative fluoroscopy proved effective in detecting and correcting malpositions across both implant types. This also reduces the likelihood of patients having to undergo a second operation. Especially in patients undergoing ACL reconstruction with the ASB implant and in whom intraoperative fluoroscopy is not accessible, it seems appropriate to perform additional control methods to ensure proper button positioning during surgery due to the high malposition rate and the possibility of needing a second surgery. We believe that our study should be supported by a larger sample size and different comparison groups.

Statement of ethics

The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (number: 2024-09/113).

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization, EA, IK.; Data curation, EA, IK, HET.; Investigation, EA, IK, HET, RB, YK.; Methodology, EA. and IK.; Project administration, EA.; Resources, EA, IK, HET, RB, YK.; Writing – original draft, EA, YK.,.; Writing – review & editing, EA, IK, HET, RB, YK.

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Comparison of the Effects of Conventional and Minimally Invasive Cardiac Surgery with Cardiopulmonary Bypass on Inflammatory, Hepatic and Renal Parameters

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Abstract

Aim: Cardiac surgery has been performed by conventional methods for many years, but in recent years, minimally invasive cardiac surgery has come to the forefront. The aim of this study was to evaluate the effects of conventional and minimally invasive cardiac surgery performed under CPB guidance on inflammatory, hepatic and renal parameters.

Methods: In this retrospective study, those who underwent conventional cardiac surgery with CPB were defined as Group 1 and those who underwent minimally invasive cardiac surgery were defined as Group 2. Descriptive data of the groups, preoperative and postoperative urea, creatinine, ALT, AST, GGT, WBC, CRP data which are indicators of inflammatory, hepatic and renal functions, and peroperative variables such as intubation time, ICU time and hospital stay time were evaluated.

Results: In this study, demographic data of the two groups were similar ($p > 0.05$). Preoperative and postoperative inflammatory, hepatic, renal parameters (urea, creatinine, WBC, CRP, AST, ALT, GGT), ICU time, hospital stay and mortality rates were also similar ($p > 0.05$). However, there were statistically significant differences between the groups in terms of duration of ACC ($p = 0.021$), total perfusion time ($p = 0.001$) and mechanical ventilation time ($p = 0.005$), and these values were higher in Group 2.

Conclusions: Minimally invasive cardiac surgery performed under CPB guidance was associated with longer ACC, total perfusion time and duration of mechanical ventilation compared to conventional cardiac surgery. However, inflammatory, renal and hepatic parameters showed similar results, although there were no significant differences.

Keywords: *Cardiopulmonary bypass; conventional bypass; minimally invasive bypass; inflammatory parameters; hepatic parameters; renal parameters*

1. Introduction

Recently, the increasing popularity of less invasive procedures has affected almost every surgical speciality, including cardiac surgery. Advances in imaging, surgical instrumentation and robotic technology have made it more usual for surgeons to perform complex cardiac surgery procedures through small incisions.[1] Cardiac surgery has been performed with conventional methods for many years, but different methods have come to the forefront in recent years. One of these is the minimally invasive cardiac surgery method. Many studies have supported many advantages of minimally invasive cardiac surgery compared to conventional approaches. These include improved cosmetic results, reduced postoperative pain levels, faster recovery time, and reduced need for blood product transfusion compared to cardiac surgery performed via sternotomy. Despite the potential advantages of minimally invasive cardiac surgery, available evidence, including randomised controlled trials and meta-analyses, has not demonstrated a significant difference in mortality between minimally invasive and conventional surgical approaches.[2-4]

In addition, there are still ongoing debates about the benefits of minimally invasive interventions[5]. Another point is that the superiority of the two methods over each other in terms of their effects on inflammation, hepatic parameters and renal parameters is controversial.

The aim of this retrospective study was to evaluate the effects of

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conventional and minimally invasive cardiac surgery performed under CPB guidance on inflammatory, hepatic and renal parameters.

2. Materials and Methods

This study is a retrospective clinical research.

2.1. Ethics Approval

In this study, approval was obtained from the institutions and the local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 22.07.2024 - Approval no: HRÜ/24.10.18). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

2.2. Study Design and Data Collection

The study included conventional and minimally invasive cardiac surgery patients who underwent CPB-guided cardiac surgery in the cardiovascular surgery clinic of Harran University Hospital between 01 January 2024 and 31 December 2024.

Those who underwent conventional cardiac surgery under CPB guidance were defined as the first group (Group 1), and those who underwent minimally invasive cardiac surgery were defined as the second group (Group 2).

Descriptive data of the groups (age, gender, height, weight, body surface area (BSA), flow, ejection fraction percentage (EF%), smoking, diabetes, hypertension, aortic cross clamp time, total perfusion time, surgical operation performed); urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), white blood count (WBC), C-reactive protein (CRP) data, which are indicators of preoperative and postoperative inflammatory, hepatic and renal functions; and duration of intubation (duration of mechanical ventilation support), duration of intensive care unit (ICU) stay, and duration of hospital stay as peroperative variables.

2.3. Inclusion and Exclusion Criteria

Patients who underwent emergency cardiac surgery, patients who were scheduled for additional cardiac surgery such as aortic aneurysm or dissection, patients who underwent repeat cardiac surgery, patients with known systemic inflammatory disease, patients with chronic liver disease, chronic kidney disease or haemodialysis patients were excluded from the study.

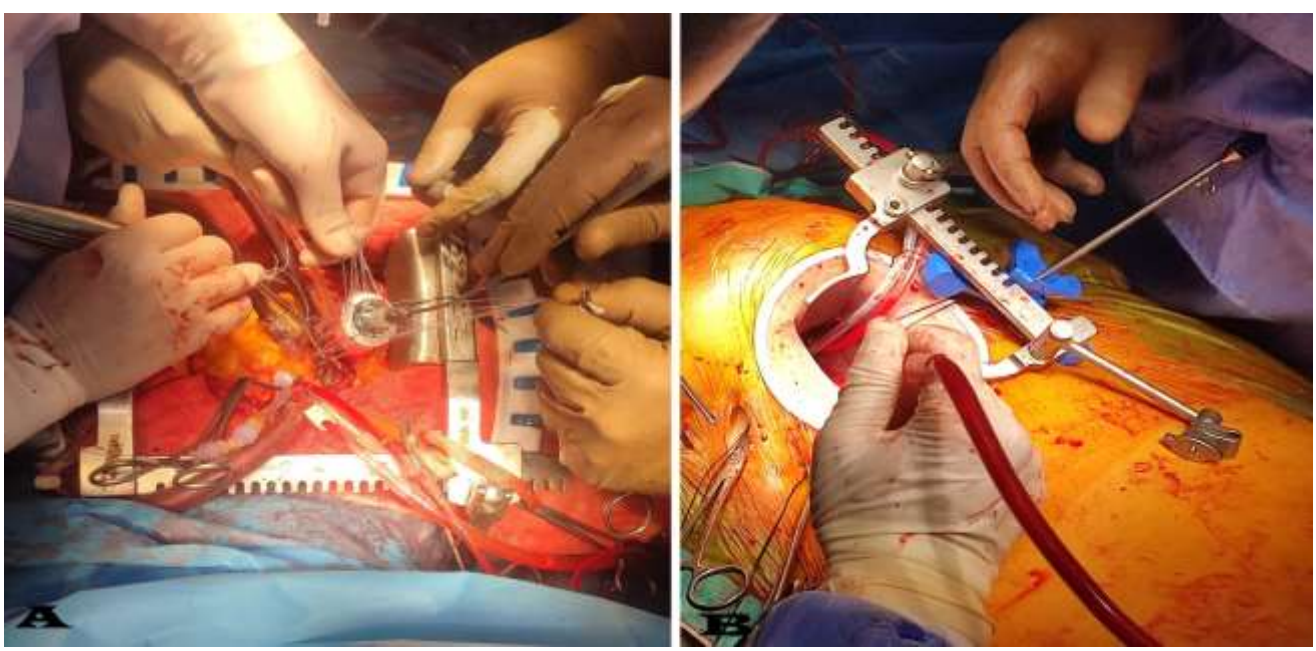
Patients of the last year in the centre where the study was performed were included consecutively after the exclusion criteria were applied. The included patients were adults aged between 18 and 85 years who underwent conventional and minimally invasive cardiac surgery under CPB guidance.

2.4. Conventional Cardiac Surgery Technique

Standard coronary and valvular heart surgery techniques were performed in all patients. After midline sternotomy in coronary heart surgery patients, arterial cannulation was performed from the ascending aorta and venous cannulation was performed from the right atrium with a single venous cannula (two stage venous conduit). Left mammary artery graft was used in all cases. Saphenous vein graft was applied to other coronary grafts. Complete revascularisation was performed in all patients. In valvular heart surgery patients, in addition to standard surgical techniques, in mitral valve replacements after midline sternotomy, arterial cannulation was performed from the ascending aorta and venous cannulation was performed with two venous cannulae from the vena cava superior and vena cava inferior (Bicaval cannulation). In aortic valve replacements, arterial cannulation was performed from the ascending aorta and venous cannulation was performed from the right atrium with a single venous cannula (two stage cannulation). Standard extracorporeal circulatory systems (heart-lung machine) were also used (Figure 1-A).

Figure 1

A: Conventional method of cardiac surgery, B: Minimally invasive cardiac surgery method



2.5. Minimally Invasive Cardiac Surgery Technique

In all patients undergoing minimally invasive cardiac surgery, arterial cannulation was performed via femoral artery and venous cannulation was performed via femoral vein and right jugular vein cannulations and cardiopulmonary bypass was performed. Cardiopulmonary bypass was performed with antegrade cardioplegia delivered from the aorta using a long cardioplegia cannula and del nido cardioplegia solution was used in all patients. In all cases, aortic clamping was performed with an aortic clamp delivered through an approximately 1 cm long incision made in the 2nd intercostal space. For patients undergoing coronary artery graft surgery, a left internal mammary artery (LIMA) graft was prepared and a special retractor was used for this procedure, followed by the use of a standard retractor for distal and proximal anastomoses. Proximal anastomoses were routinely performed to the aorta under aortic cross clamp.

Coronary artery graft surgery was performed through an approximately 5 cm long incision starting from the left 4th intercostal space adjacent to the sternum; aortic valve replacement was performed through an approximately 5 cm long incision starting from the right 2nd or 3rd intercostal space adjacent to the sternum; and mitral valve replacement was performed through a relatively lateral approximately 5 cm long incision in the right 5th intercostal space (Figure 1-B).

In all minimally invasive cardiac surgery patients, 1 thoracic drainage tube and 1 flat drain placed adjacent to the aorta were used as standard. In all minimally invasive operations, patients were intubated with a double lumen intubation tube as standard, the lung on the side of the approach was deflated, and standard endotracheal intubation was returned at the end of the operation.

2.6. Statistical Analyses

Statistical analyses were conducted using the SPSS® 17.0 computer programme (version 17.0, SPSS, Chicago, IL, USA). Means and standard deviations were calculated for continuous data. Kolmogorov Smirnov test and Shapiro-Wilk test were used to evaluate normality distribution. Student T test and Mann Whitney U tests were used to evaluate normal and non-normally distributed data, respectively. Frequency and percentage analyses were performed for nominal data and Chi-Square test and Chi-Square corrected test were used for comparison. A 'p' value less than 0.05 was considered statistically significant.

3. Results

Although certain differences were observed between the two groups in terms of variables such as age, body weight and EF%, statistical analyses showed that these differences were not significant ($p > 0.05$). Furthermore, no statistically significant differences were found between the groups in terms of gender distribution, types of surgical procedures, smoking and prevalence of chronic diseases ($p > 0.05$). These findings indicate that both groups were similar in terms of basic demographic and clinical characteristics (Table 1).

Table 1

Demographic and descriptive data of the groups

Variables		Group 1 N=51	Group 2 N=42	Test Statistics	P
Age (Year) (Mean±SD)		61.25±9.61	66.35±7.05	-2.863	0.075 [a]
Height (cm) (Mean±SD)		171.70±9.06	170.21±9.76	0.762	0.609 [a]
Weight (kg) (Mean±SD)		81.62±11.99	75.52±14.93	2.186	0.096 [a]
BSA (Mean±SD)		1.93±0.14	1.86±0.18	1.946	0.055 [a]
Flow (L) (Mean±SD)		4.64±0.18	4.47±0.66	1.768	0.080 [a]
Preoperative % EF (Mean±SD)		51.62±8.48	44.80±10.23	3.513	0.223 [a]
Gender (n, %)	Male	30, (58.8%)	28, (66.7%)	0.604	0.437 [b]
	Female	21, (41.2%)	14, (33.3%)		
Surgical Type (n, %)	*CABGx1	4, (7.8%)	5, (11.9%)	3.586	0.610 [c]
	*CABGx2	6, (11.8%)	8, (19.0%)		
	*CABGx3	20, (39.2%)	12, (28.6%)		
	*CABGx4	12, (23.5%)	12, (28.6%)		
	· AVR	5, (9.8%)	4, (9.5%)		
	· MVR	4, (7.8%)	1, (2.4%)		
Smoking (n, %)	· None	35, (68.6%)	33, (78.6%)	1.159	0.282 [b]
	· Yes	16, (31.4%)	9, (21.4%)		
Hypertension (n, %)	· None	14, (27.5%)	17, (40.5%)	1.758	0.185 [b]
	· Yes	37, (72.5%)	25, (59.5%)		
COPD (n, %)	· None	45, (90.2%)	38, (90.5%)	0.000	1.000 [c]
	· Yes	5, (9.8%)	4, (9.5%)		
Diabetes Mellitus (n, %)	· None	27, (52.9%)	22, (52.4%)	0.003	0.957 [b]
	· Yes	24, (47.1%)	20, (47.6%)		
Hyperlipidemia (n, %)	· None	31, (60.8%)	30, (71.4%)	1.156	0.282 [b]
	· Yes	20, (39.2%)	12, (28.6%)		

[a]: Independent sample T-test, [b]: Chi-Square Test, [c]: Chi-square corrected test, Mean±SD: Mean±Standard Deviation, n: Frequency, %: Percent, BSA: Body Surface Area, EF: Ejection Fraction, COPD: Chronic Obstructive Pulmonary Disease.

Table 2

Comparison of inflammatory, hepatic, renal parameters and early clinical results of the groups

Variables	Group 1 N=51 (Mean±SD)	Group 2 N=42 (Mean±SD)	Test Statistics	P
Preoperative urea (mg/dL)	28.71±12.08	31.46±12.81	-1.064	0.290 [a]
Postoperative urea (mg/dL)	40,96±18,85	43,98±19,24	-0.936	0.349 [d]
Preoperative creatine (mg/dL)	0.91±0.25	0.94±0.27	-0.390	0.698 [a]
Postoperative creatine (mg/dL)	0.97±0.39	1,01±0.43	-0.479	0.632 [d]
Preoperative WBC (10^3µl)	6,95±2,93	7,04±3,28	-0.035	0.972 [d]
Postoperative WBC (10^3µl)	8,75±4,66	7,65±3,75	-0.967	0.333 [d]
Preoperative CRP (mg/L)	2,23±3,58	2,25±3,72	-0.116	0.908 [d]
Postoperative CRP (mg/L)	29,65±32,77	26,11±31,52	-0.405	0.685 [d]
Preoperative AST (U/L)	46,60±40,06	44,47±40,89	-0.421	0.674 [d]
Postoperative AST (U/L)	86,07±84,34	85,64±87,03	-0.085	0.932 [d]
Preoperative ALT (U/L)	29,50±21,92	27,78±17,73	-0.151	0.880 [d]
Postoperative ALT (U/L)	39,43±46,39	37,42±41,31	-0.093	0.926 [d]
Preoperative GGT (IU/L)	24.37±14.38	29.14±20.24	-1.325	0.188 [a]
Postoperative GGT (IU/L)	34,76±20,20	35,78±19,02	-0.340	0.734 [d]
ACC time (min)	56.17±19.59	64.50±18.40	-2.306	0.021 [d]
Total perfusion time (min)	94.52±34.46	118.54±45.10	-3.329	0.001 [d]
Mechanical ventilation support time (hours)	6.86±2.32	8.88±3.72	-2.805	0.005 [d]
ICU time (days)	2.68±0.86	2.69±1.27	-0.669	0.504 [d]
Duration of Hospitalisation (days)	11.80±3.51	10.35±4.74	1.689	0.095 [a]
Mortality (Postoperative 30-day period)	0.00±0.00	0.02±0.15	-1.102	0.270 [d]

[a]: Independent sample T-test, [d]: Mann-Whitney U test, Mean±SD: Mean±Standard Deviation, WBC: White blood count, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ACC: Aortic cross clamp, ICU: Intensive Care Unit.

As shown in Table 2, there was no statistical difference between the groups in terms of preoperative and postoperative inflammatory, hepatic, renal parameters (urea, creatinine, WBC, CRP, AST, ALT, GGT), ICU time, hospital stay and mortality rates and the results were similar ($p > 0.05$). However, there were statistically significant differences between the groups in terms of aortic cross clamp (ACC) time ($p = 0.021$), total perfusion time ($p = 0.001$) and mechanical ventilation time ($p = 0.005$) and these values were higher in Group 2 (Table 2).

4. Discussion

This study aimed to compare the effects of conventional and minimally invasive cardiac surgery performed under CPB guidance on inflammatory, hepatic and renal parameters. In the study, important findings were obtained in the comparison of demographic, clinical and postoperative variables between two different patient groups. Although certain differences were observed in some variables such as age, weight and EF% between the two groups, no statistically significant difference was found. However, a statistically significant increase was observed in Group 2 in terms of ACC time, total perfusion time and mechanical ventilation time, which are of great importance in CPB-guided cardiac surgery ($p < 0.05$). These results suggest that the surgical process lasted longer in Group 2 and the postoperative recovery process of the patients required more support. These findings show the superiority of our study. There was no significant difference between the two groups in terms of length of hospital stay, ICU stay and mortality rates. This indicates that postoperative care processes were similar for both groups and there was no significant change in complication rates. There was no significant difference between the groups in terms of preoperative and postoperative biochemical parameters (urea, creatine, GGT, WBC, CRP, AST, ALT). These results suggest that the metabolic responses before and after surgery are similar.

Compared with previous studies, it has been suggested that prolongation in the duration of ACC and total perfusion time may increase the risk of postoperative complications.[6-8] However, no significant difference in mortality was found in this study, indicating that surgical and postoperative care was managed effectively for both groups. Therefore, despite the longer perfusion times and duration of mechanical ventilation, there was no significant difference in the overall postoperative course of the patients.

In terms of haematological and biochemical parameters, no significant difference was found between the groups in terms of preoperative and postoperative WBC and CRP levels. However, the literature suggests that the use of CPB triggers systemic inflammatory response syndrome (SIRS), which may be associated with postoperative complications. However, it has been reported that minimally invasive surgery is associated with smaller surgical incision and lower inflammatory response.[9,10] In our study, the minimally invasive surgery group had lower WBC and CRP levels, although not statistically significant. Our findings support this literature data and suggest that minimally invasive surgery has the potential to reduce the inflammatory process.

In terms of hepatic and renal parameters, preoperative and postoperative AST, ALT, GGT, urea and creatinine levels were not significantly different between the groups. However, an increase in AST and ALT levels was observed in both groups in the postoperative period. Plasma AST and ALT levels are within normal limits in the healthy population. These parameters are usually affected by coronary heart disease, impaired renal function and various drugs.[11] This reflects the effect of CPB on hepatic and renal functions. In our study, hepatic and renal functions were better

preserved in the minimally invasive cardiac surgery group, but this difference was not statistically significant.

There are many studies in the literature comparing conventional and minimally invasive cardiac surgery.[12-19] However, there is still no consensus on the results.

Akowuah et al.[12] compared minithoracotomy and conventional sternotomy methods in mitral valve repair. In their study, they compared the safety and efficacy of minithoracotomy and sternotomy mitral valve repair. As a result of their study, they reported that minithoracotomy was not superior to conventional sternotomy in the recovery of physical function at 12 weeks. They also reported that minithoracotomy provided valve repair at high rates and quality and had similar safety results to conventional sternotomy at 1 year.[12] Bratt et al.[13] compared the bleeding rates of the two methods in minimally invasive and conventional aortic valve replacement. At the end of their study, they reported that minimally invasive aortic valve replacement did not lead to less bleeding-related outcomes compared to complete sternotomy[13]. Similarly, Hancock et al.[14] compared mini sternotomy with conventional sternotomy for aortic valve replacement in their study. At the end of their study, they reported that aortic valve replacement performed by mini sternotomy did not decrease red blood cell transfusion within 7 days after surgery compared with conventional sternotomy.[14] Telyuk et al.[15] reported that there was no significant difference between limited mini sternotomy and conventional sternotomy in terms of all-cause mortality, reoperation rate, myocardial infarction, coronary vascularisation or death from any cause (MACE events) and echocardiographic data at a median follow-up of 6.1 years.[15] There are studies showing different results from these studies.[16-19] One of these studies is the study by Filip et al.[16] In their study, they compared the perioperative and postoperative results of aortic valve replacement operations performed by conventional full sternotomy and partial upper sternotomy in isolated aortic valve replacement. As a result of their study, they reported that ministernotomy in aortic valve replacement did not increase morbidity and mortality and significantly decreased postoperative blood loss and shortened hospital stay. They also stated that ministernotomy can be used successfully as an alternative method to sternotomy.[16] Another study in the literature states that minimally invasive aortic valve replacement provides equivalent results at a lower cost compared to conventional aortic valve replacement. The study also reported that the mortality and morbidity results of the two methods were similar. However, it was also reported that minimally invasive aortic valve replacement was associated with a decrease in ventilator time, blood product use, early discharge and total hospital cost.[17] In another study, similar to our study, it was reported that minimally invasive cardiac surgery was associated with longer CPB times. However, they reported that the incidence of low cardiac output syndrome and atrial fibrillation was lower in minimally invasive cardiac surgery.[18] In a study investigating the effect of these two methods on quality of life, it was reported that ministernotomy provided a faster improvement in quality of life and satisfaction in the first month compared to full sternotomy.[19]

When the data in our study and different studies in the literature are evaluated, it is thought that there is a need for further research on these two methods.

4.1. Limitations

This study has several important limitations. Firstly, the single-centre and retrospective design of the study limits the generalisability of the findings. This structure may limit the direct applicability of the results in other centers, given the surgical protocols, patient management strategies and standards of care applied in different institutions. Furthermore, possible selection bias during patient selection cannot be ruled out; in particular, the fact that patients eligible for minimally invasive surgery are selected according to specific clinical criteria may create imbalance in comparative analyses.

The level of experience of the surgical teams and technical differences may also have affected the results; this variability could not be controlled. In addition, more comprehensive analyses were not possible due to the lack or inadequacy of some laboratory and clinical parameters. In line with these limitations, the findings of this study should be interpreted with caution and should be supported by prospective, prospective, multicenter and randomised controlled trials.

5. Conclusion

In conclusion, minimally invasive cardiac surgery performed under CPB guidance was associated with longer ACC time, total perfusion time and mechanical ventilation time compared to conventional cardiac surgery. In this respect, conventional cardiac surgery is still considered superior. However, although there were no significant differences in inflammatory, renal and hepatic parameters, they showed similar results. Future randomised controlled trials with larger patient groups will contribute to a better understanding of these findings.

Statement of ethics

In this study, approval was obtained from the institutions and the local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 22.07.2024 - Approval no: HRÜ/24.10.18). The study was conducted following the principles of the Declaration of Helsinki. Since only anonymized patient data was used and there was no risk or impact on patient care, informed consent was not required. This consent waiver was approved by the Institutional Review Board and Ethics Committee and complies with regulatory and ethical guidelines for retrospective studies.

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

MZB and BA is the major contributor to the writing of the manuscript. MZB and BA are involved in the design, conception, data collection and analysis of the study. All authors read and approved the final version of the manuscript.

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The Association between SGLT2 Inhibitors Use and the Risk of Contrast Induced Acute Kidney Injury in Patients with Type 2 Diabetes

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Abstract

Aim: Contrast-induced acute kidney injury (CI-AKI) is associated with increased risk of morbidity and mortality and specific treatments are needed. In our study, we aimed to investigate the association of sodium-glucose cotransporter-2 inhibitors (SGLT2-I) use with the development of CI-AKI due to coronary angiography (CAG) in patients with DM.

Methods: A total of 516 type 2 diabetes mellitus (DM) patients, including 250 SGLT2-I users and 266 non-SGLT2-I users, were included in our retrospective and cross-sectional study.

Results: The study groups were divided into CI-AKI (+) and CI-AKI (-). SGLT2-I use was statistically significantly higher in the CI-AKI (-) group. Multivariate logistic regression analysis showed that SGLT2-I use reduced the probability of CI-AKI by 83.8%.

Conclusions: Our findings suggest that SGLT2-Is may significantly reduce the risk of CI-AKI in diabetic patients undergoing CAG. In conclusion, the use of SGLT2-I may have a protective and preventive effect against the development of CI-AKI.

Keywords: *Contrast-induced acute kidney injury; coronary angiography; diabetes mellitus; percutaneous coronary intervention; sodium-glucose cotransporter-2 inhibitors*

1. Introduction

Percutaneous coronary intervention (PCI) is a successful treatment option for patients with coronary artery disease. In addition to its proven benefits, this procedure can also lead to some adverse events. Contrast-induced acute kidney injury (CI-AKI) is a type of acute kidney injury that occurs after the administration of contrast media for elective coronary angiography (CAG). This condition is characterised by an increase in serum creatinine levels ≥ 0.5 mg/dl or a 25% increase from baseline 48 hours after contrast media administration. The incidence ranges from 1.3% to 33.3% and is the third most important cause of hospital-acquired renal failure. CI-AKI is closely associated with longer hospital stays, more frequent readmissions and increased risk of short- and long-term morbidity and mortality. Type 2 diabetes mellitus (DM) is one of the risk factors for CI-AKI.[1,2]

Several mechanisms have been demonstrated for renal impairment after contrast media administration. The cytotoxicity of contrast media triggers apoptosis and necrosis of tubular and endothelial renal cells. The concentration and duration of the contrast medium play an important role in this process. After contrast media administration, ischaemia and hypoxic changes occur due to renal haemodynamic disturbances. Inflammatory processes and oxidative stress play a role in the deterioration of renal function.[3,4]

Although various approaches including hydration, N-acetylcysteine, sodium bicarbonate and statins have been investigated to prevent CI-AKI, the optimum approach has not yet been clearly determined.[5,6] Sodium-glucose cotransporter-2 inhibitors (SGLT2-I) are a new class of oral anti-diabetic agents.

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SGLT2-Is act by inhibiting renal reabsorption of glucose, increasing renal glucose excretion and reducing serum glycaemic levels. These drugs reduce blood pressure, the risk of cardiovascular events and kidney disease in patients with and without diabetes.[7,8] Two randomised controlled trials, the DAPA-CKD[9] and EMPA-Kidney[10] studies, have shown that in patients with chronic kidney disease, regardless of the presence or absence of diabetes, gliflozins lead to a lower risk of chronic kidney disease progression and death from renal or cardiovascular events compared with placebo. SGLT2-Is are thought to preserve renal function by inhibiting inflammation and fibrosis, reducing oxidative stress and improving tubular oxygen content. These mechanisms ultimately delay the decline in renal function and slow the progression of proteinuria.[11,12]

In recent years, several studies have been conducted to evaluate the effect of SGLT2-Is on contrast-induced nephropathy. Recent observational studies have suggested that SGLT2-Is may prevent CI-AKI in patients with diabetes undergoing coronary interventions such as CAG and PCI.[13,14] However, there are also studies that have not shown a clear nephroprotective effect of SGLT2-Is after PCI.[15] To our knowledge, there are few clinical studies focused on this issue. Since specific treatments for CI-AKI are still needed in the clinic, it is necessary to find a new treatment strategy that is an important complement to the current clinical management protocol. In our study, we aimed to investigate the association of SGLT2-I use with the development of CI-AKI due to PCI and CAG in patients with DM.

2. Materials and Methods

2.1. Study Population and Laboratory Measurements

A total of 516 type 2 DM patients, 250 of whom were using SGLT-2 inhibitors and 266 of whom were not using SGLT2-I, were included in our retrospective and cross-sectional study, and whose medical history and previous examinations did not prevent their inclusion in the study, and who were scheduled for CAG due to elective indications. Patients using SGLT2 for 6 months or more were included in the study. Patients between 01.01.2023 and 31.12.2024 were included in the study. Patients using dapagliflozin 10 mg or empagliflozin 10 mg were included in the study. Diabetes mellitus was defined as fasting blood sugar level ≥126 mg/dL or HbA1c level ≥6.5% or treatment with antidiabetic medication [16]. CI-AKI was defined as a 0.5 mg/dL increase in serum creatinine concentration 48 hours after contrast medium administration or a 25% increase in creatinine level from baseline [2].

Patients received standard hydration with intravenous infusion of 0.9% saline at a rate of 1 mL/kg/h for 12 hours before and 12 hours after the procedure. Patients who were administered other anti-CI-AKI drugs such as N-acetylcysteine and sodium bicarbonate were excluded from the study. Patients who received the same contrast material during coronary angiography were included in the study. In patients with unstable angina pectoris, myocardial infarction, chronic kidney disease, heart failure, malignancy, pregnant women were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. Adana City Training and Research Hospital Ethics Committee approved the study with decision number 2231 dated 03.11.2022. After 5 minutes of rest, in a dim and quiet environment, blood pressure measurements were taken from both arms using a suitable cuff and pulses were monitored. Anthropometric body weight measurements were performed. Height was measured with the feet bare and together, leaning perpendicular to the height measurement ruler. BMI was calculated as body weight (kg) divided by the square of height in meters (BMI=kg/m2). Laboratory procedures of the study were performed in the Biochemistry Laboratory of Adana City Training and Research Hospital. Venous blood was drawn from the antecubital vein after at least 8 hours of overnight fasting from the patients and the control group during routine controls. Laboratory measurements of participants were measured using automated laboratory methods (Abbott Aeroset, Minneapolis, MN) and appropriate commercial kits (Abbott).

2.2. Statistical analysis

We used SPSS 24.0 (Chicago, IL, USA) for all of our statistical analysis. We checked for normality in the distribution of continuous variables using the Kolmogorov-Smirnov test. The mean ± standard deviation was used to express continuous variables in the group data. The numerical and percentage values for the categorical variables were used. When comparing groups with normally distributed continuous variables, either Student's t-test or one way anova were employed. When comparing continuous variables that did not follow a normal distribution, the Mann-Whitney U test was employed. To compare categorical variables, the chi-square ($\chi 2$) test was employed. We identified the independent variables that have an effect on CI-AKI. Statistically significant parameters with a p value less than 0.05 were used in the multivariate logistic regression analysis that followed the univariate model in the independent determination of patients with CI-AKI. Statistical significance level was accepted as $p<0.05$.

3. Results

The study groups were divided into CI-AKI (+) and CI-AKI (-). There were 37 patients with CI-AKI (+) and 479 patients with CI-AKI (-). When both groups were compared according to demographic, clinical and laboratory findings; age, duration of DM, BMI, LDL level, total procedure time and amount of contrast medium were found to be statistically significantly higher in the CI-AKI (+) group. SGLT2-I utilisation was statistically significantly higher in the CI-AKI (-) group (table 1).

Patients with CI-AKI (-) were divided into three groups according to SGLT2-I use: SGLT2-I non-users, dapagliflozin users and empagliflozin users. When the groups were compared, it was found that the rate of CI-AKI (-) was higher in the group receiving dapagliflozin and empagliflozin compared to the group not using SGLT2-I. No statistically significant difference was found between the groups receiving empagliflozin and dapagliflozin in terms of CI-AKI (-) rate (table 2).

To determine whether the patients were CI-AKI (+), multivariate logistic regression analysis was performed using parameters with a p value less than 0.05 and shown to be statistically significant in univariate analysis. According to multivariate logistic regression analysis, SGLT2-I use reduced the probability of CI-AKI by 83.8%. Each 1 unit increase in BMI increased the probability of CI-AKI by 12% (table 3).

4. Discussion

In our study, we aimed to evaluate the effect of SGLT2-I use on the risk of CI-AKI formation after elective CAG in patients with type 2 DM. The main findings of our study were that SGLT2-I use was higher in the CI-AKI (-) group than in the CI-AKI (+) group and SGLT2- I use reduced the probability of CI-AKI by 83.8%. The reno-protective effect of SGLT2-I drugs in patients with type 2 DM is known. However, data on the effect of SGLT2-Is on CI-AKI in patients undergoing CAG are limited. SGLT2-Is, which are used in patients with type 2 DM and have known renoprotective properties, may also have favourable effects on the development of CI-AKI after CAG.

Table 1

Demographic and descriptive data of the groups

Variables	CI-AKI (+) n=37	CI-AKI (-) n=479	p
Gender (F/M), n	16/21	233/246	0.532
Age (year)	60.38±10.93	53.64±14.36	0.001
Diabetes mellitus duration (year)	3.3±1.91	2.7±1.65	0.036
Body mass index (kg/m2)	29.3±5.8	26.14±5.96	0.002
Systolic blood pressure (mmHg)	128.35±10.49	128.2±11.35	0.939
Diastolic blood pressure (mmHg)	89.92±5.2	90.26±5.12	0.694
Smoking, n	18(48.6%)	237(49.5%)	0.923
Hypertension, n	16(43.2%)	218(45.5%)	0.79
ACEi/ ARB use, n	13(35.1%)	182(38%)	0.73
Beta bloker use, n	4(10.8%)	68(14.2%)	0.568
Calcium channel blockers use, n	3(8.1%)	36(7.5%)	0.896
Statin use, n	14(37.8%)	169(35.3%)	0.755
SGLT2-I use, n	8(21.6%)	242(50.5%)	<0.001
White blood cell (10^3/ µL)	8.14±2.7	8.39±2.6	0.589
HbA1c, %	7.67±1.1	7.36±1.48	0.116
Red blood cell (106/ µL)	4.3±0.94	4.25±0.78	0.745
Hemoglobin(g/dL)	12.07±2.12	11.94±2.06	0.728
Platelet (10^3/ µL)	270.72±69.6	284.48±101.1	0.423
Fasting plasma glucose (mg/dL)	168.35±54.67	157.77±55.33	0.263
Thyroid stimulating hormone (mIU/L)	2.04±1.9	1.74±1.23	0.447
Blood Urea Nitrogen (mg/dL)	24.89±4.78	24.74±3.81	0.854
Creatinine (mg/dL)	0.8±0.13	0.77±0.18	0.176
Albumin (g/dl)	3.88±0.54	3.8±0.56	0.465
Total protein (g/dL)	6.91±0.71	6.88±0.61	0.826
C-reactive protein (mg/L)	0.75±0.75	1.06±1.05	0.167
Sodium (mmol/L)	136.74±5.07	136.2±4.31	0.474
Potassium (mmol/L)	4.4±0.69	4.53±0.66	0.272
Uric acid (mg/dL)	5.16±1.68	5.69±2.05	0.169
Triglycerides (mg/dL)	161.91±65.13	154.64±56.34	0.487
High-density lipoprotein (mg/dL)	28.76±9.7	46.63±43.48	0.023
Low-density lipoprotein (mg/dL)	149.39±24.54	124.36±37.17	<0.001
Alanine aminotransferase (u/L)	15.3±10.01	16.9±9.96	0.352
Alanine aminotransferase (u/L)	19.47±5.67	20.96±8.22	0.347
Calcium (mg/dL)	9.07±0.62	8.92±0.66	0.193
25-hydroxyvitamin D (ng/mL)	13.01±4.09	17.55±13.52	0.319
eGFR (mL/min/1.73 m2)	90±0.56	89.88±2.05	0.728
The total processing time (min)	24.16±4.66	18.82±3.08	<0.001
Amount of contrast (cc)	106.75±15.1	87.20±7.70	<0.001

CI-AKI: Contrast-induced Acute Kidney Injury, DM: Diabetes mellitus, eGFR: estimated glomerular filtration rate, HbA1c: glycated haemoglobin, ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blocker, SGLT2-I: sodium glucose cotransporter 2 inhibitors

CI-AKI has become one of the leading causes of iatrogenic kidney injury, which is closely associated with poorer prognosis and higher overall healthcare costs in patients. Common risk factors of CI-AKI have been reported to include traditional risk factors (age, chronic renal failure, heart failure and DM) and factors such as dosage and types of contrast agents, multiple operations within a short period of time. Therefore, patients with DM are at higher risk of developing CI-AKI after an elective CAG and should be given special attention.[17] The mechanisms underlying how contrast media induce CI-AKI and impair renal function encompass a variety of pathogenic processes that are not fully understood. Three main mechanisms such as medullary hypoxia, oxidative stress and inflammation are reported to be involved simultaneously.[18] Recent studies suggest that SGLT2-Is play an important role beyond glucose regulation, including inhibition of inflammation, oxidative stress reduction and prevention of medullary hypoxia.[19] These findings increase interest in studying the effects of this class of drugs on renal function tests in patients with cardiovascular diseases.

DECLARE-TIMI, DAPA-CKD and EMPA-KIDNEY studies demonstrated the renoprotective effect of dapagliflozin and empagliflozin in patients with chronic renal failure regardless of the presence or absence of diabetes.[7,9,10] In a study conducted in type 2 DM patients,

Table 2

Evaluation of patients with CI-AKI (-) according to SGLT2-I use

Variable	SGLT2-I (-) n=266	Dapagliflozin use n=139	Empagliflozin use n=111	p
CI-AKI (-)	237 (89.0%) α, β	135 (97.1%)	107 (96.4%)	0.003

CI-AKI: Contrast-induced Acute Kidney Injury, SGLT2-I: sodium glucose cotransporter 2 inhibitors, α: Significant association between the SGLT2-I (-) group and Dapagliflozin group ($p<0.05$), β: Significant association between the SGLT2-I (-) group and Empagliflozin group ($p<0.05$)

Table 3

Multivariate logistic regression analysis for detection of patients with CI-AKI (-)

Variables	Odds Ratio	95 % Confidence Interval	p
Age (year)	1.042	0.980-1.108	0.193
Diabetes mellitus duration (year)	1.215	0.895-1.649	0.211
Body mass index (kg/m2)	1.120	1.034-1.212	0.005
SGLT2-I use	0.162	0.044-0.596	0.006

SGLT2-I: sodium glucose cotransporter 2 inhibitors, CI-AKI: Contrast-induced Acute Kidney Injury

Nadkarni et al. aimed to compare the risk of AKI in relation to SGLT2-I with non- users and did not observe an increased risk of AKI in DM patients receiving SGLT2-I compared to non-users during the 18-month follow-up period. Moreover, the study reported that the risk of AKI decreased in the group treated with SGLT2-I.[20] In an in vivo study conducted in a rat model, Huang et al. reported the potential molecular mechanism by which dapagliflozin may reduce CI-AKI by regulating the HIF-1a/HE4/NF-kB pathway.[21] Huang et al. found that the risk of CI-AKI was reduced in patients with DM who used SGLT2-I.[22] Liu et al. showed that dapagliflozin effectively reduced the risk of CI-AKI and showed renoprotective effects in patients with type 2 DM and chronic renal failure undergoing elective CAG.[17] In their randomised controlled study, Hosseini et al. reported that empagliflozin significantly reduced the incidence of CI-AKI in patients undergoing PCI by improving renal function parameters such as eGFR and cystatin C.[23] In a meta-analysis performed by Rodriguez et al., it was shown that the use of SGLT2-I significantly reduced the risk of CI-AKI by up to 63% in diabetic patients undergoing CAG or PCI.[24] In a study conducted by Özkan et al. in DM patients with non-ST segment elevation myocardial infarction, SGLT2-I use may be protective against the development of CI-AKI, especially in patients with comorbid conditions such as DM.[14]

In our study, we found that the use of SGLT2-I may be protective against the development of CI-AKI. We found that the use of SGLT2-I reduced the probability of CI-AKI by 83.8%. SGLT2-I may reduce renal oxygen consumption by directly inhibiting SGLT2- mediated sodium reabsorption in the proximal tubule and alleviate renal hypoxia by increasing blood ketone levels to provide more substrates for mitochondrial energy metabolism. On the other hand, it may exert renoprotective effect by regulating tubuloglomerular feedback responses and vasodilatation of afferent arterioles by improving glomerular hyperfiltration. In addition, SGLT-2-I reduces the energy requirement of the nephron. One of the reasons why the development of CI-AKI was significantly less in patients receiving SGLT2-I in our study may be that it reduces the energy required in the renal system, makes energy utilisation more efficient and alleviates renal hypoxia. One of the mechanisms leading to CI-AKI is a reduction in renal plasma flow to the outer medulla. This ischaemia is due to an imbalance between renal vasodilatory and vasoconstrictive factors. SGLT2-I may help to correct volume loss and expand the intravenous volume by causing natriuresis, glycosuria and subsequent diuretic action. This increases the clearance of contrast media, decreases the concentration of contrast media in the tubule lumen and vasa recta and may prevent the activation of neurohormonal systems leading to medullary vasoconstriction.[14,22] In our study, there was no difference in the use of ras blockers and statins between the groups with and without CI-AKI. The fact that the use of ras blockers, which are known to slow down diabetic kidney disease progression, and statins, which have studies on preventing CI-AKI, were similar in both groups is important in showing that the use of SGLT2-I provides an additional contribution. Phase studies show that the use of SGLT2-I treatment for more than 6 months may reveal beneficial effects of cardiac and renal protection in patients with DM. Therefore, we used 6 months of SGLT2-I use as the inclusion cut-off for participants in this study. The effect of shorter duration of SGLT2-I use on the incidence of CI-AKI needs to be evaluated in future studies. We found no difference in the development of CI-AKI with the use of empagliflozin or dapagliflozin among SGLT2-Is. This suggests that SGLT2-Is may be effective in the development of CI-AKI as a group effect. In our study, we found that LDL levels were higher in the CI-AKI group than in the non-CI-AKI group. High LDL may aggravate the CI-AKI condition by increasing atherosclerosis formation, mitochondrial damage and mitochondrial oxidative stress.

Risk factors for the development of CI-AKI include age, chronic renal failure, heart failure, diabetes, obesity, dosage of contrast agents and duration of the procedure. As the duration of diabetes increases, vascular smooth muscle cell functions and endothelial functions deteriorate. This has been shown to cause atherosclerosis, impaired nitric oxide-mediated vasodilatation and inflammatory cell migration. In our study, the correlation between the increase in the duration of diabetes mellitus and the development of CI-AKI is consistent with the literature. In our study, we found that age, BMI, LDL level, amount of contrast medium and total procedure time of CAG were higher in the group with CI-AKI, again consistent with the literature. The amount of contrast medium and procedure time are important for the development of CI-AKI. In our study, although the amount of contrast medium and procedure time were longer in the group that developed CI-AKI, the fact that the amount of contrast medium and procedure time were not statistically significant in the logistic regression analysis performed to determine the development of CI-AKI shows that the use of SGLT2-I reduces the development of CI-AKI independently of these two factors. This finding is important.

Development of is a complication that increases hospital stay, mortality and morbidity rates despite successful PCI. Although many factors predicting the development of CI-AKI after CAG or PCI have been described in the literature, widely accepted treatment options for the prevention of CI-AKI are insufficient CI-AKI.[3] Pre- and post-procedural hydration therapy and high-dose statin therapy before the procedure are effective methods in CI-AKI prophylaxis. In addition, there are limited data in the literature showing that amlodipine, theophylline and phosphodiesterase-5 inhibitors may be useful.[25] On the other hand, SGLT2-I is a group of drugs that are part of the current treatment of patients with diabetes and whose cardioprotective and nephroprotective effects have been strongly recognised in the light of recent studies. SGLT2-I may be useful for renal

protection in patients who will undergo elective coronary intervention, in patients who will be exposed to contrast media and in diabetic patients who are predicted to have a high risk of developing CI-AKI due to comorbidities.

Our study had some limitations. Our study was single-centre and retrospective. Further multicentre studies with a larger number of patients are needed. In our study, we used a definition of CI-AKI based on the change in creatinine value, which is generally accepted in the literature. Another limitation is that neutrophil gelatinase-associated lipocalin and cystatin C, which are more specific laboratory markers of CI-AKI, were not evaluated.

5. Conclusion

Our findings suggest that SGLT2-Is may significantly reduce the risk of CI-AKI in diabetic patients undergoing CAG or PCI. In conclusion, SGLT2-I use may have a protective and preventive efficacy against the development of CI-AKI. SGLT2-I may be an important and promising option for the clinical management of CI-AKI in patients with DM.

Statement of ethics

Adana City Training and Research Hospital Ethics Committee approved the study with decision number 2231 dated 03.11.2022.

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

HAO, EG, DDO, FNA, is the major contributor to the writing of the manuscript. HAO, BSA, BI, BBK, IA, CD, AGM, CY, TS, HES are involved in the design, conception, data collection and analysis of the study. All authors read and approved the final version of the manuscript.

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Evaluation of Irrational Antibiotic Use in Patients Presenting to Çukurova University Faculty of Dentistry

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Abstract

Aim: Rational drug use has gained increasing importance in recent years. In our country, the use of antibiotics for dental problems is generally high. This study aims to investigate the unnecessary use of antibiotics for dental issues.

Methods: In this descriptive and cross-sectional study, patients over the age of 18, with no mental disorders, who presented with dental complaints to Çukurova University Faculty of Dentistry between January 2024 and October 2024 were included. In addition to routine examinations, patients were assessed in the Department of Oral and Maxillofacial Radiology to determine the necessity of antibiotic use. The frequency values of the collected data were calculated. The chi-square test or Fisher's exact test was applied to analyze relationships between variables. The significance level was set at $p<0.05$.

Results: A total of 109 female and 101 male individuals participated in the study, with a mean age of 39.4±15.3 years. Among the patients, 90% were found to use antibiotics unnecessarily, while 83% insisted on doctors prescribing antibiotics. Additionally, 35% of antibiotic users did not adhere to the recommended duration prescribed by the doctor, and 82.4% did not check the expiration dates of the antibiotics. Unnecessary antibiotic use was significantly associated with education level, income status, and the presence of systemic diseases.

Conclusions: The rate of unnecessary antibiotic use for dental problems is alarmingly high. These findings highlight the necessity of effectively managing patient demands and enhancing patient education in the antibiotic prescription processes of clinical practice.

Keywords: *Antibiotics; dentistry; antibiotic resistance; self medication*

1. Introduction

The irrational and unnecessary use of medications is a significant global issue. According to the World Health Organization (WHO), more than half of all medicines worldwide are inappropriately prescribed, dispensed, or consumed, and nearly half of the patients fail to use these medications correctly. Additionally, it is reported that one-third of the world's population lacks access to essential medicines.[1] In 1985, the WHO introduced the concept of "Rational Use of Medicines" (RUM), defining it as the process in which "patients receive medications appropriate to their clinical needs, in the right doses, for an adequate duration, and at the lowest cost to both themselves and society".[1] The misuse of antibiotics, particularly in non-bacterial infections and inappropriate doses, is classified as irrational medication use.

The overuse of medications, especially antibiotics, has gained global attention in recent years. Inappropriate and excessive antibiotic use poses a significant challenge worldwide and in our country. One of the most critical consequences of improper antibiotic usage is the development of antibiotic resistance.[2] In our country, the rate of antibiotic consumption has increased significantly since these medications became covered by health insurance.[3] As of 2024, antibiotics remain the most consumed drugs in terms of both cost and volume.[4] Among Southeast European countries, our nation has the highest rate of antibiotic use.[5] Dentistry is a healthcare field where antibiotics and analgesics are commonly prescribed. Antibiotics in dental treatments are not first-line therapies but are rather used as adjuncts when systemic symptoms are present. Antibiotic treatment is indicated in cases such as fever, lymphadenopathy, fatigue, malaise, and trismus, while symptoms like pain and swelling alone do not justify their use.[6] Antibiotic prophylaxis is recommended for immunosuppressed

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patients, those with infective endocarditis, metabolic disorders, indwelling catheters or shunts, mitral valve prolapse, or prosthetic heart valves. Acute conditions requiring antibiotic therapy include necrotizing ulcerative gingivitis, stage 3-grade C/incisor molar pattern periodontitis, acute periapical abscess, cellulitis, pericoronitis, and infections spreading into the deep fascial spaces of the head and neck.[7] In our country, antimicrobial agents are prescribed in 82.4% of dental prescriptions.[8] This rate is 4.2% in Belgium, 9% in Wales, and 11.3% in Canada.[9–11] A study conducted in Izmir revealed that 74.4% of antibiotic use among 203 dental patients was unnecessary.[12] Current data on the unnecessary use of antibiotics for dental problems in our country are limited, and there is a need for updated, community-based field studies on this issue. This study aims to determine the prevalence of unnecessary antibiotic use among patients with dental problems and to identify the underlying reasons for this issue.

2. Materials and Methods

This descriptive and cross-sectional study was conducted in compliance with the principles outlined in the 1964 Declaration of Helsinki and approved by the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Çukurova University (Date: December 8, 2023; Meeting No: 139; Decision No: 19). Patients who visited the Faculty of Dentistry at Çukurova University between January 2024 and October 2024, were over 18 years of age, used antibiotics for dental reasons, had no mental disorders, and voluntarily agreed to complete the study form were included. All participants were examined by an experienced clinician following a standardized diagnostic protocol, including anamnesis, intraoral and extraoral examinations, and panoramic radiographic evaluation where necessary.

Table 1

Distribution of data by gender

		Gender			
		Female(%)	Male (%)	Total(%)	*p*
Education Level	No Education	4(3.7)	4(4)	8(3.8)	0.852
	Primary School	22(20.2)	21(20.8)	43(20.5)	
	Middle School	24(22)	26(25.7)	50(23.8)	
	High School	34(31.2)	33(32.7)	67(31.9)	
	University	25(22.9)	17(16.8)	42(20)	
Income Status	Income higher than expenses	17(15.6)	11(10.9)	28(13.3)	0.551
	Income equal/close to expenses	51(46.8)	47(46.5)	98(46.7)	
	Expenses higher than income	41(37.6)	43(42.6)	84(40)	
Systemic Disease	None	77(70.6)	80(79.2)	157(74.8)	0.507
	Hypertension	5(4.6)	4(4)	9(4.3)	
	Cardiological Disease	7(6.4)	2(2)	9(4.3)	
	Diabetes Mellitus	7(6.4)	6(5.9)	13(6.2)	
	Other	13(11.9)	9(8.9)	22(10.5)	
Antibiotic Necessity	Necessary	11(10.1)	10(9.9)	21(10)	0.963
	Unnecessary	98(89.9)	91(90.1)	189(90)	
Where was the antibiotic prescribed?	Family Health Center	29(26.6)	37(36.6)	66(31.4)	<0.001*
	Oral and Dental Health Center	37(33.9)	26(25.7)	63(30)	
	State Hospital	-†	14(13.9)	14(6.7)	
	Private Hospital	4(3.7)	1(1)	5(2.4)	
	Private Dental Clinic	33(30.3)†	15(14.9)	48(22.9)	
	Other	6(5.5)	8(7.9)	14(6.7)	
How was the antibiotic prescribed?	Prescribed by the physician as necessary	11(10.1)	10(9.9)	21(10)	0.782
	Prescribed upon patient request/insistence	92(84.4)	83(82.2)	175(83.3)	
	Not prescribed by the physician	6(5.5)	8(7.9)	14(6.7)	
How was the antibiotic used?	Used until completion as recommended by the physician/pharmacist	65(59.6)	71(70.3)	136(64.8)	0.106
	Used until symptoms subsided	44(40.4)	30(29.7)	74(35.2)	
Checking the Expiration Date	Yes	23(21.1)	14(13.9)	37(17.6)	0.169
	No	86(78.9)	87(86.1)	173(82.4)	
Total		109(100)	101(100)	210(100)	

*n(%). Chi-square or Fisher's exact test (*p<0.05). † indicates a statistically significant difference between the columns (†p values corrections with Bonferroni method).*

Table 2

Distribution of Data by Antibiotic Necessity

		Antibiotic Necessity			
		Necessary (%)	Unnecessary (%)	Total(%)	*p*
Education Level	Middle school or below	3(14.3)	98(51.9)	101(48.1)	0.001*
	High School or Higher	18(85.7)	91(48.1)	109(51.9)	
Income Status	Income higher than expenses	7(33.3)	21(11.1)	28(13.3)	<0.001*
	Income equal/close to expenses	14(66.7)	84(44.4)	98(46.7)	
	Expenses higher than income	-	84(44.4)	84(40)	
Systemic Disease	None	8(38.1)	149(78.8)	157(74.8)	<0.001*
	Present	13(61.9)	40(21.2)	53(25.2)	
Who prescribed the antibiotic?	Dentist	13(61.9)	98(51.9)	111(52.9)	0.165
	Medical Doctor	8(38.1)	63(33.3)	71(33.8)	
	Self-medicated	-	28(14.8)	28(13.3)	
Where was the antibiotic prescribed?	Family Health Center	3(14.3)	63(33.3)	66(31.4)	
	Oral and Dental Health Center	7(33.3)	56(29.6)	63(30)	
	State Hospital	-	14(7.4)	14(6.7)	
	Private Hospital	5(23.8)	-	5(2.4)	
	Private Dental Clinic	6(28.6)	42(22.2)	48(22.9)	
	Other	-	14(7.4)	14(6.7)	
Where was the antibiotic prescribed?	FMC/SH/PH	8(38.1)	77(40.7)	85(40.5)	0.377
	OHDC/PDC	13(61.9)	98(51.9)	111(52.9)	
	Other	-	14(7.4)	14(6.7)	
How was the antibiotic used?	Used until completion as recommended by the physician/pharmacist	15(71.4)	121(64)	136(64.8)	0.500
	Used until symptoms subsided	6(28.6)	68(36)	74(35.2)	
Checking the Expiration Date	Yes	5(23.8)	32(16.9)	37(17.6)	0.544
	No	16(76.2)	157(83.1)	173(82.4)	
Total		21(100)	189(100)	210(100)	

*n(%). Chi-square or Fisher's exact test (*p<0.05). FHC: Family Health Center, ODHC: Oral and Dental Health Center, PDC: Private Dental Clinic, PH: Private Hospital, SH: State Hospital*

All patients provided written informed consent prior to participation in the study. Exclusion criteria were defined as having hearing, visual, or speech impairments, psychiatric disorders, or declining participation in the study. Patients who completed the form were examined in the Department of Oral Diagnosis and Maxillofacial Radiology, and the necessity of their antibiotic use was recorded. The form collected the following data: Demographic information: age, gender, education level, and income status; systemic disease history; antibiotic usage information: necessity, place of prescription, method of prescription, method of use, and whether the expiration date was checked.

The patients' age was summarized as mean ± standard deviation (min–max), while other data were presented as frequencies and percentages. Relationships between categorical variables were analyzed using the Chi-square test or Fisher's exact test. When a significant relationship was detected, column ratios were compared to determine the parameter causing the significance (p-values were adjusted using the Bonferroni method). A significance level of p<0.05 was considered. Statistical analyses were performed using SPSS 20.0 software (Chicago, IL, USA).

3. Results

A total of 210 individuals participated in the study, including 109 women (mean age: 40.1 ± 15.9, min: 18, max: 69) and 101 men (mean age: 38.7 ± 14.7, min: 18, max: 66), with an overall mean age of 39.4 ± 15.3 (min: 18, max: 69). The prevalence of the analyzed variables by gender is presented in Table 1. Among the participants, 51.9% had a high school education or higher, and 46.7% reported income levels equal to or close to their expenses. Additionally, 74.8% of the participants had no systemic diseases, and 90% of the patients were found to use antibiotics unnecessarily. Antibiotics were most frequently prescribed at primary healthcare centers (31.4%), oral and dental health centers (30%), and private dental clinics (22.9%). A statistically significant relationship was observed

between gender and the location where antibiotics were prescribed (p<0.001). Upon evaluating the significant associations, it was found that antibiotics were prescribed more frequently in state hospitals for male patients (13.9%) compared to female patients (0%). Conversely, in private dental clinics, antibiotics were prescribed more frequently for female patients (30.3%) than for male patients (14.9%). Furthermore, 83.3% of the patients reported requesting or insisting on antibiotics, 35.2% used antibiotics only until their symptoms subsided, and 82.4% did not check the expiration date of the antibiotics.

The prevalence of the data examined according to the necessity of antibiotic use is shown in Table 2. There was a significant relationship between education status and antibiotic necessity (p=0.001). In patients with secondary school or lower education level, unnecessary antibiotic use (51.9%) was significantly higher than necessary use (14.3%), while unnecessary antibiotic use (48.1%) was significantly lower than necessary use (85.7%) in patients with high school or higher education level. There was a significant relationship between income status and necessity of antibiotic use (p<0.001). In those whose income exceeded their expenses, unnecessary antibiotic use (11.1%) was significantly lower than necessary use (33.3%), while in those whose expenses exceeded their income, unnecessary antibiotic use (44.4%) was significantly higher than necessary use (0%). Unnecessary antibiotic use was significantly higher in those without systemic disease than in those with systemic disease (p<0.001). There is no significant relationship between where the antibiotic is prescribed, how it is used, and whether the patient checks the expiration date of the antibiotic and the necessity of using the antibiotic (p>0.05).

4. Discussion

This study highlights the prevalence of unnecessary antibiotic use among patients with dental problems. According to the findings, 90% of participants who used antibiotics for dental reasons were using them unnecessarily, 83.3% insisted on being prescribed antibiotics, and 82.4% did not check the expiration dates of the antibiotics they used. Antibiotics were most commonly prescribed at primary healthcare centers (31.4%), oral and dental health centers (30%), and private dental clinics (22.9%), primarily by dentists (52.9%) and physicians (33.8%).

Consistent with some studies in the literature, our study also found no significant difference in unnecessary antibiotic use between genders. However, considering previous findings indicating that women generally tend to use medications more frequently, the absence of such a difference in our study may be attributed to the sample size or the demographic characteristics of our study population.[13–15]

In this study, unnecessary antibiotic use was significantly higher among patients with a middle school or lower education level (51.9%) compared to those with appropriate use (14.3%). Similarly, Şengül and Aykıl, in their evaluation of the rational use of medicines scale, found that individuals with postgraduate education levels achieved the highest scores.[16] In the study conducted by Çanakçı and Çanakçı, no significant relationship was found between socioeconomic status and patients who used antibiotics unnecessarily for dental problems.[13] These differences are thought to stem from variations in the populations studied and the sampling methods used. A significant difference was observed in antibiotic use based on patients' income levels in this study. However, no significant difference was reported in studies conducted in Aydın and at Trakya University.[13,16] These discrepancies may be attributed to regional differences and the numerical evaluation of income in the Trakya University study, which differs from the approach used in this research. The use of necessary antibiotics for dental diseases was found to be significantly higher among individuals with chronic illnesses. However, Şengül and Akyıl's study did not report a significant difference.[16]

In Southern (16%) and Eastern European (19%) countries, dental problems are the second most common reason for self-medication with antibiotics after upper respiratory infections.[17] In Cameroon, 21.2% of individuals used antibiotics for dental issues without consulting a doctor.[18] Similarly, in Pakistan, 57% of individuals with dental problems reported self-medicating.[19] In Izmir, only 49.3% of patients visiting a dental faculty stated that they always used medication as prescribed by a doctor.[20] In Mersin, 31.3% of patients visiting family health centers reported obtaining medications without a prescription.[21] In Istanbul, 39% of patients reported using medications without consulting a dentist[14] while this rate was 57.2% in Adana, with 34.3% of these medications being antibiotics.[22] In Ankara, the rate was 64.3%.[23] Despite the ban on the sale of antibiotics without a prescription under the Rational Use of Medicines initiative in our country, this measure has paradoxically led to an increase in antibiotic use.[3] Patients frequently insist on being prescribed antibiotics, and in this study, 83.3% of participants reported doing so. Similarly, Gül et al. found that 64% of patients insisted on antibiotic prescriptions, with 69.4% of them stating that their requests were fulfilled. Although physicians are knowledgeable about rational drug use, the increased workload and reduced consultation times contribute to higher rates of antibiotic prescriptions.[24]

In a study conducted at Trakya University, 51% of antibiotics were prescribed at oral and dental health centers, while 45% were prescribed at family health centers.[13] Among the antibiotics prescribed at oral and dental health centers, 9% were deemed necessary, compared to 8% of those prescribed at family health centers. A significant difference was observed in the necessity of antibiotic prescriptions between oral and dental health centers and family health centers.[13] In the present study, although no significant difference was observed, 33.3% of antibiotics prescribed at oral and dental health centers and 14.3% of those prescribed at family health centers were found to be necessary.

In a study conducted in Istanbul, 50% of patients reported using medication for the duration recommended by their doctor.[14] However, in the study by Yapıcı et al., 43.7% of patients stated that they discontinued the medication earlier than recommended.[21] Similarly, in Adana, 36.5% of patients reported stopping antibiotics before finishing the prescribed course.[22] In Özçelikay's study, 23.9% of patients indicated that they did not use medications for the recommended duration.[25]

One limitation of this study is that it was conducted in a single-center and included all patients regardless of specific symptoms. The single-center design of this study may limit the generalizability of the findings. Therefore, future multi-center studies involving diverse geographic regions and socioeconomic groups are recommended. Other limitation of this study is that it did not include data on the exact timing of antibiotic use in relation to symptom onset. Future studies may investigate whether the day of initiation affects the necessity of antibiotic use. However, as demonstrated in the findings, a key strength of the study is the collaboration between family physicians and dentists, who are the primary prescribers of antibiotics. Moreover, these findings may contribute to the development of health policies focused on managing patient demands, regulating prescription practices, and enhancing public awareness. Additional strengths of this study include its relatively large and gender-balanced sample size, the multidimensional evaluation of antibiotic use behavior and the analysis of associations with education level, income status, and systemic disease presence.

5. Conclusion

Irrational drug use remains a significant issue in our country. Despite various legal regulations aimed at addressing this problem, the desired outcomes have not been achieved. Unnecessary antibiotic use persists, driven by patient insistence and the heavy workload of physicians. Irrational antibiotic use is particularly prevalent in dentistry. To prevent inappropriate antibiotic use, the primary focus should be on educating patients. As evidenced by the findings in the literature, the problem is not limited to unnecessary prescriptions; patients also fail to adhere to recommended dosages and durations of use. The findings may also serve as a guide in shaping national antibiotic use policies. This highlights the need for comprehensive strategies to promote rational drug use and enhance patient compliance.

Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Date: December 8, 2023; Meeting Number: 139; Decision No: 19) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Author contributions

HDY: Study design, data collection or processing, statistical analysis, writing. AIC: Study design, concept, literature search, writing.

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Do childhood measles and DTaP vaccination decrease the mortality rate caused by SARS CoV-2 in OECD countries?

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Abstract

Aim: This study aims to examine the relationship between DTaP (diphtheria, tetanus, pertussis) and measles vaccination rates in the Organization for Economic Co-operation and Development (OECD) countries and the case fatality rate (CFR) caused by SARS CoV-2.

Methods: Considering that the COVID-19 pandemic primarily affected the northern hemisphere and due to seasonal effects, OECD countries located in the northern hemisphere were included in this study. 2018 OECD data were used for vaccination rates, while the "Our World in Data" website (https://ourworldindata.org/) was used for CFR and other data. CFR was calculated based on the total mortality count of OECD countries for the 3-month period following the first confirmed SARS CoV-2 case.

Results: Based on the correlation between vaccination rates and 3-month CFR in OECD countries, a negative, although not yet significant, correlation (r = -0.264, p = 0.145) was found between CFR and DTaP vaccination rates, and a statistically significant negative correlation (r = -0.479, p = 0.006) between CFR and measles vaccination rates.

Conclusions: It was concluded that SARS CoV-2 CFRs are lower in countries with stricter implementation of measles vaccination, a live-attenuated vaccine. Governments should implement stronger vaccination programs to promote widespread immunization.

Keywords: *Case fatality rate; SARS CoV-2; vaccination; DTaP; measles*

1. Introduction

SARS CoV-2 (severe acute respiratory syndrome coronavirus 2), which emerged in Wuhan province, China, at the end of 2019, has become a pandemic affecting the entire world. While this study focuses on the early phase of the pandemic, prior to the availability of effective vaccines or treatments, COVID-19 mortality rates have varied across countries. Over 500,000 people have died globally. Factors such as government interventions, public compliance, average age of affected individuals, the number of tests conducted, and a country's healthcare infrastructure have all influenced SARS CoV-2 mortality.[1] While children are generally at risk for many contagious diseases, they have been less affected by the SARS CoV-2 pandemic. As of May 12, 2020, data from New York City Health indicated nine deaths in the 0–17 age group, with six involving underlying comorbidities.[2] According to a report by the Center for Evidence-Based Medicine (CEBM), mortality in children under the age of 9 was low, estimated at approximately 1% in China.[3] One explanation is their faster immunological response. Childhood vaccination is considered a primary factor for this rapid response and also plays a key role in maintaining herd immunity.

The pertussis vaccine, an inactivated vaccine, has been administered as a single shot since the 1930s and as part of the DTaP combination (diphtheria-tetanus-pertussis) since the 1990s. Although DTaP vaccination programs have been strictly implemented in OECD countries in recent years, the coverage rate was around 80% during the 2000s.[5] The measles vaccine, first developed in 1963, has been widely used in the USA since the 1980s

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as part of the Centers for Disease Control and Prevention (CDC)'s initiative to eliminate measles among children.[5] The UK introduced the measles vaccine, a live-attenuated vaccine, in 1988, and other OECD countries gradually incorporated it into their immunization schedules. Since its introduction, the incidence of measles has decreased significantly. It is typically administered in combination with mumps and rubella vaccines as the MMR vaccine.[6]

In this study, we aim to examine the relationship between childhood vaccination rates for DTaP and measles and the case fatality rate (CFR) from SARS CoV-2 across OECD countries.

Table 1

Data obtained in the first 3 months from the first case in the country

Country	Case fatality ratio, %	Total number of tests	Total confirmed deaths
France	18	724574	21856
Belgium	16	396052	7844
United Kingdom	14	2620000	37048
Italy	14	1980000	27967
Holland	13	344334	5856
Sweden	12	119400	2586
Spain	11	1350000	24824
Slovenia	7	82161	108
Ireland	7	325795	1639
Greece	6	160991	172
Canada	5	717451	2560
United States	5	4030000	40682
Switzerland	5	376935	1641
Denmark	5	480239	563
Austria	5	405341	8257
Polond	4	967177	1092
Portugal	4	840681	1424
Finland	4	99090	199
Lithuania	4	287982	66
Germany	4	2450000	5750
Estonia	4	80720	65
Czech Republic	3	449356	320
Norway	3	234637	235
Luxembourg	3	72996	110
Japan	3	162816	393
Turkey	3	2450000	4729
Latvia	2	111404	24
Korea	2	563035	236
Slovakia	2	185596	28
Israel	2	531569	279
Hungary	1	195894	534
Iceland	1	60450	10

2. Materials and Methods

Considering the fact that the COVID-19 pandemic was mainly observed in the northern hemisphere and due to seasonal effects, OECD countries located in the northern hemisphere (Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States) were included in this study. OECD countries located in the southern hemisphere (Australia, Chile, Colombia, Mexico, New Zealand) were excluded from the study. 2018 OECD data were used for the vaccination rates, while the "Our World in Data" website (https://ourworldindata.org/) was used for CFR and other related data. CFR was calculated based on the total mortality count in OECD countries for the 3-month period starting from the date when the first SARS CoV-2 case was reported.

2.1. Statistical Analysis

The data obtained from the study were recorded in SPSS 24.0 (Armonk, NY: IBM Corp.). The data of the patients are expressed as median (quartiles) for distributed data and percentage for categorical variables. Shapiro Wilk test was used to check if the continuous variables were normally distributed. While comparing the vaccination rates between the case fatality groups caused by COVID-19, the Mann-Whitney U test was used. Chi-square test or Fisher test was used to analyze the categorical variables. The correlation analyses for the vaccination rates and CFR were performed using Spearman tests. $P < 0.05$ was considered to be statistically significant.

Table 2

Vaccination rates by country

Country	Diphtheria, tetanus, pertussis, % of children	Measles, % of children
France	96.0	90.0
Belgium	98.0	96.0
United Kingdom	94.0	92.0
Italy	93.0	93.0
Holland	93.0	93.0
Sweden	97.0	97.0
Spain	97.0	97.0
Slovenia	93.0	93.0
Ireland	92.0	92.0
Greece	97.0	97.0
Canada	91.0	90.0
United States	92.0	92.0
Switzerland	95.0	95.0
Denmark	95.0	95.0
Austria	95.0	95.0
Polond	93.0	93.0
Portugal	99.0	99.0
Finland	99.0	96.0
Lithuania	92.0	92.0
Germany	95.0	97.0
Estonia	92.0	87.0
Czech Republic	96.0	96.0
Norway	96.0	96.0
Luxembourg	99.0	99.0
Japan	99.0	97.0
Turkey	96.0	96.0
Latvia	96.0	98.0
Korea	98.0	98.0
Slovakia	97.0	96.0
Israel	98.0	98.0
Hungary	99.0	99.0
Iceland	91.0	93.0

3. Results

As per the data obtained from 32 OECD countries included in this study, it has been seen that France is the country with the highest CFR rate (18%) followed by Belgium (16%), UK (14%), Italy (14%), Holland (13%), Sweden (12%) and Spain (11%) while Hungary and Iceland are the countries with the lowest CFR rates (1%) (Table 1).

Considering the DTaP vaccination rates of the countries it has been determined that Japan (99%), Luxemburg (99%), Portugal (99%), Finland (99%) and Hungary (99%) have the highest rates whereas Canada (91%) and Iceland (91%) have the lowest rates. Considering the Measles vaccination rates of the countries it has been determined that Portugal (99%), Luxemburg (99%) and Hungary (99%) have the highest rates whereas Canada (90%) and Estonia (87%) have the lowest rates (Table 2).

As per the vaccination rates of the countries that have been divided into groups (light, medium, heavy) according to the CFR and significance levels between the groups it has been stated that vaccination with DTaP does not create a significant difference between the groups (96.5%, 94.0%, 94.5%; p=0.255) whereas measles vaccination creates a significant difference between the groups (96.0%, 94.0%, 93.0%; p=0.048) (Table 3).

When examined the correlation levels between vaccination rates of OECD countries and 3-month CFR it has been seen that there is negative although not yet significant correlation (r=-264.0, p=0.145) between CFR and DTaP vaccination rates and there is negative correlation at a high level of significance between CFR and measles vaccination rate (r=-0.479, p=0.006) (Table 4, Figure 1).

Table 3

Vaccination rates and inter-group significance levels of countries that are divided into groups (low, medium, high) by case fatality rates

	Low (<% 5), median (quartiles)	Medium (≥5, <10), median (quartiles)	High (≥10), median (quartiles)	p
Diphtheria, tetanus, pertussis	96.5 (95.2-99.0)	94.0 (92.0-96.0)	94.5 (93.0-96.2)	0.255
Measles	96.0 (94.5-98.0)	94.0 (92.0-95.0)	93.0 (92.0-97.0)	0.048

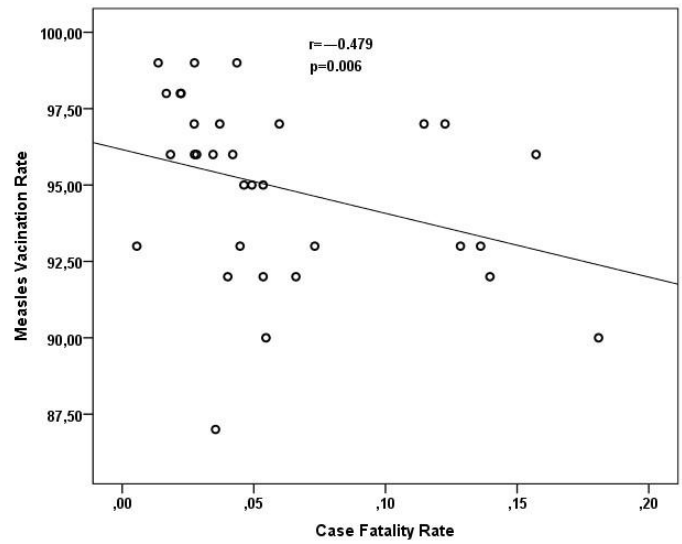
Table 4

Vaccination rates and inter-group significance levels of countries that are divided into groups (low, medium, high) by case fatality rates

	Correlation coefficient	P
Diphtheria, tetanus, pertussis	-264.0	0.145
Measles	-0.479	0.006

Figure 1

The correlation of between case fatality rate and measles vaccination rate.



4. Discussion

In the current study, a negative, though not yet statistically significant, correlation was observed between DTaP vaccination rates and SARS CoV-2 CFR, while a significant negative correlation was found between measles vaccination and CFR in OECD countries. One hypothesis for the lower mortality in SARS CoV-2-infected younger individuals is that childhood vaccination programs, which have become increasingly widespread over the past fifty years, may contribute to stronger immune responses.

Gold et al. investigated MMR (measles, mumps, rubella) vaccination rates in Italy, the UK, France, the United States, and Germany in 2002.[7] Their findings showed the highest MMR rate in Germany and the lowest in Italy, the UK, and France. A negative correlation between 2002 MMR rates and SARS CoV-2 CFRs as of 3 May 2020 was reported. Our findings based on 2018 OECD data align with this. Measles vaccination rates in Italy, the UK, and France were below 95% (93%, 92%, and 90%, respectively), while Germany's was 97%. Corresponding CFRs within three months of the first reported case were 14%, 14%, and 18% for Italy, the UK, and France, and 4% for Germany. The article also referenced Madagascar, where a nationwide MMR campaign had just concluded before the pandemic. As of 4 May 2020, the country had reported 1,443 cases and 13 deaths within three months of the first detected case on 20 March 2020. Although climate factors in the southern hemisphere may influence viral transmission, the country's low CFR (0.9%) may also be attributed to the recent mass vaccination campaign.[8]

In a study of 131 countries, BCG vaccination was associated with markedly lower COVID-19 mortality. Countries without BCG programs experienced approximately ten times more deaths (40/million) than those with active programs (4.28/million).[9]

Live-attenuated vaccines such as BCG and measles are thought to provide broad immunological benefits beyond their target pathogens. These vaccines may enhance innate immune training and generate non-specific immune memory, potentially increasing

resistance to unrelated infections such as SARS CoV-2.[10,11] This mechanism might explain the protective association observed between higher measles vaccination rates and lower CFRs in our study. Supporting this, previous research suggested that vaccinated children in China were significantly less affected by COVID-19, likely due to cross-reactivity from rubella or measles immunization.[12]

However, CFR is influenced by multiple factors beyond vaccination, including public health policies, testing strategies, and healthcare infrastructure. For instance, Sweden's CFR is four times higher than Norway's, despite similar vaccination coverage. Iceland, with below-average measles vaccination rates, had the lowest CFR among OECD countries—likely due to rigorous testing and isolation protocols. Iceland had the highest testing rate per capita among OECD nations.[13]

4.1. Limitations

The limitation of our study is that situations which may directly affect the CFR, such as the policies followed by countries in preventing the epidemic, health infrastructures, and the number of tests performed during the COVID-19 epidemic, vary from country to country. In addition, the fact that countries differ significantly in terms of population, and that epidemic control in highly populated countries is much more difficult than in low-populated countries such as Iceland, also affects the CFR. These reasons impact the results of the statistical analysis.

5. Conclusion

Considering the fact that child patients are less affected than adults, the positive effects of cross-resistances on the immune system formed by live-attenuated vaccines, and the key result of our study, which is the significant negative correlation between the live-attenuated measles vaccine and CFR, it has been stated that live-attenuated vaccines have a decreasing effect on CFR caused by SARS CoV-2. To conclude, healthcare implementers in countries should spread childhood vaccination across the entire society and implement these practices with stricter programmes.

Statement of ethics

In this research, data obtained from the web was analyzed. For this reason, ethics committee approval was not obtained.

Since our study was planned retrospectively, an informed consent form was not required.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers

Author contributions

Dr. RG, Dr. AA, Dr. GE, Dr. SYS, Dr. MIS, Dr. BSA: conceptualization, methodology, investigation, and writing – original draft. Dr. RG, Dr. AA, Dr. GE, Dr. SYS, Dr. MIS, Dr. BSA: resources, formal analysis, and writing – review and editing. Dr. RG, Dr. AA, Dr. GE, Dr. SYS, Dr. MIS, Dr. BSA: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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Correlation of lower extremity functional scale and electrodiagnostic findings in patients with sciatic neuropathy

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Abstract

Aim: Sciatic nerve has an essential role in sensorimotor innervation of the lower extremities. This study explored the association between electrophysiological findings and lower extremity function in patients with sciatic neuropathy.

Methods: This retrospective study analyzed the electrophysiological data of 41 patients with sciatic neuropathy who underwent evaluation between January 2023 and August 2024. Lower extremity function was evaluated with the Lower Extremity Functional Scale (LEFS), while neuropathic pain was assessed using the Douleur Neuropathique 4 (DN4) questionnaire.

Results: The median LEFS score was 29, reflecting significant functional impairment, while 95.1% of patients exhibited neuropathic pain based on DN4 scores. LEFS scores showed a significant correlation with the compound muscle action potential (CMAP) amplitudes of the abductor hallucis brevis (Spearman rho: 0.52, $p < 0.001$) and extensor digitorum brevis (Spearman rho: 0.32, $p = 0.04$) muscles.

Conclusions: This study provides novel evidence on the critical role of posterior tibial and peroneal nerve dysfunction in lower extremity impairment in sciatic neuropathy patients. The stronger correlation of LEFS with posterior tibial nerve function underscores its importance in high-effort activities. We propose that electrophysiological findings may facilitate a more objective evaluation of functional impairment in sciatic neuropathy patients and aid in the development of targeted rehabilitation strategies.

Keywords: *Sciatic neuropathy; lower extremity; neuropathic pain; electromyography; nerve conduction studies*

1. Introduction

The sciatic nerve is the longest and largest nerve originating from the lumbosacral plexus and is essential for the innervation of the lower extremity muscles. Sciatic neuropathy (SN) is the second most prevalent neuropathy affecting the lower limbs since it is vulnerable to injury at various locations along its extensive anatomical pathway.[1] Etiologies of SN may include penetrating trauma, bone fractures, gluteal intramuscular inject-ions, pelvic or hip surgeries, hip dislocation, surgical positioning, tumor or hematoma compression, piriformis syndrome, auto-immune processes, inflammation, radiation, and ischemia [2].

Electrophysiological assessments are essential for diagnosing sciatic neuropathies and localizing the injury site.[1] While electrophysiological research in this area is limited, available studies generally indicate that axonal damage frequently affects the sciatic nerve or its branches, predominately in the peroneal division.[3,4] Prior research has demonstrated that compound muscle action potentials (CMAP) of the tibial and peroneal nerve and sensory nerve action potentials (SNAP) of the sural nerve correlate with prognosis and the severity of neuropathic pain.[4–7] Furthermore, some studies suggest that the extent of neurogenic involvement observed in needle electromyography (EMG) examinations may vary according to the etiology of SN, distinguishing injection neuropathy from other causative factors.[3,6]

The Lower Extremity Functional Scale (LEFS) was developed to assess the functional status of the lower extremities in individuals with musculoskeletal disorders.[8] Evidence from the literature indicates that the LEFS can be reliably employed in clinical practice to assess the impact of various conditions on lower extremity function.[9]

Sciatic neuropathies can compromise lower extremity function

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through sensory-motor deficits and neuropathic pain. However, the impact of sciatic neuropathy on LEFS has not been specifically investigated. This study seeks to bridge this gap in the literature. We sought to evaluate the relationship between clinical and electrophysiological aspects of sciatic neuropathy and the LEFS. Considering that the sciatic nerve has an essential role in the sensory-motor innervation of the lower extremity, we hypothesized that certain electrophysiological findings associated with SN could significantly affect LEFS outcomes.

2. Materials and Methods

This retrospective study was conducted through analysis of patients who were referred to the electrophysiology laboratory of the Neurology Department at Adana City Training and Research Hospital with a preliminary diagnosis of sciatic neuropathy between January 2023 and August 2024. The study received approval from the local ethics committee (Registration number:118/15.08.2024).

2.1. Subjects

Clinical and demographic data, neurological examination findings, etiology and time since injury (in months), electrodiagnostic test results, and radiological findings were documented. Patients diagnosed with sciatic neuropathy were included in the study if they fulfilled all of the following criteria:

1- Weakness of lower extremity muscles innervated by the sciatic nerve or its branches, including knee flexion and foot dorsiflexion/eversion or plantar flexion/inversion
2- Sensory disturbances in areas supplied by the sciatic nerve or its branches, including the dorsum of the foot/lateral leg, sole of the foot, or posterolateral leg
3- Abnormalities of at least two branches of the sciatic nerve (posterior tibial, peroneal, or sural) in nerve conduction studies (NCS)
4- Needle EMG abnormalities in at least one muscle innervated by the sciatic nerve or its branches

Exclusion criteria included any of the following:

1- Evidence of peripheral neuropathy on electro-physiological examination or a condition likely to cause peripheral neuropathy (e.g., diabetes mellitus)
2- Findings from electrodiagnostic tests or radiological imaging consistent with lumbosacral radiculopathy or plexopathy

Lower extremity functions were evaluated using the validated Turkish version of the Lower Extremity Functional Scale [10]. This scale includes 20 items, each scored on a 5-point scale from 0 to 4, resulting in a total score of 80; higher scores reflect better functional capacity [8]. Douleur Neuropathique 4 (DN4) questionnaire was utilized to evaluate neuropathic pain, which comprises ten items with a cut-off score of four.[11,12]

2.2. Electrophysiological Evaluation

All electrophysiological evaluations were performed by authors, following protocols similar to those used in previous studies.[6,13] Electrodiagnostic evaluations were conducted with the Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA). Surface electrodes were utilized for both stimulation and recording in nerve conduction studies. Electrodiagnostic tests were conducted if the limb temperature was ≥ 32°C; extremities below this temperature were warmed. NCS were carried out bilaterally on the lower extremities. Bandpass filters for sensory and motor NCS set to 20 Hz–2 kHz and 20 Hz–10 kHz, respectively. The sweep speed and sensitivity settings were set to 1 ms/10 µV per division for sensory studies and 5 ms/2 mV for motor studies, respectively. SNAP and CMAP amplitudes were measured from peak to peak.

Antidromic sensory NCS was performed to record sural and superficial peroneal nerve SNAPs. CMAP was recorded from the abductor hallucis brevis (AHB) muscle for the posterior tibial nerve and the extensor digitorum brevis (EDB) and tibialis anterior (TA) muscles for the peroneal nerve. The reference values for NCS from our prior research were used to define the normal limits [14,15]. NCS results were considered abnormal if either CMAP or SNAP was absent, outside the normal range, or if the amplitude was less than 50% of the corresponding nerve on the contralateral lower extremity. Based on previous studies [4,15]. CMAP and SNAP amplitudes were graded as follows: Grade 1: CMAP or SNAP amplitudes are within normal reference limits and exceed 50% of the amplitude in the contralateral limb; Grade 2: CMAP or SNAP amplitudes are within normal reference limits but are less than 50% of the amplitude in the contralateral limb; Grade 3: CMAP or SNAP amplitudes are below the lower reference limit; Grade 4: CMAP/SNAP amplitudes are absent.

Needle EMG was performed using a concentric needle electrode (length = 50 mm, diameter = 0.46 mm; Bionen Medical Devices, Florence, Italy). Bandpass filters was set at 10 Hz-10 kHz. The bandpass filter was set to 10 Hz-10 kHz. Positive sharp waves and fibrillation potentials were evaluated with a sensitivity of 100 µV/division and a sweep speed of 10 ms/division during resting. Motor unit action potentials (MUAP) were analyzed during mild muscle contraction, with a sensitivity between 500-1,000 µV/division and a sweep speed of 10 ms/division. MUAPs were classified as neurogenic if the duration exceeded 15 ms and the amplitude was greater than 4 mV. Depending on the patient's tolerance level, needle EMG was applied to the tibialis anterior, medial gastrocnemius (MG), peroneus longus (PL), both short and long heads of the biceps femoris, vastus lateralis, gluteus medius, and gluteus maximus muscles. Paraspinal muscles at levels L3, L4, L5, and S1 were examined if lumbosacral radiculopathy was suspected. Additionally, saphenous and femoral nerve conduction studies were performed, and needle EMG was applied to the vastus lateralis, adductor longus, and iliopsoas muscles in cases with suspected lumbosacral plexopathy. The needle EMG examination was considered abnormal if there were acute (positive sharp waves and fibrillation potentials) or chronic (increased MUAP duration and amplitude) neurogenic findings in the evaluated muscle.

2.3. Statistical Analysis

Statistical analysis was conducted using SPSS version 20 (IBM, Armonk, New York). Shapiro-Wilk test was utilized to evaluate the normality of data distribution. Categorical data are presented as numbers and percentages (%). Numerical variables with a normal distribution are presented as mean ± standard deviation (SD), while other variables are presented as medians and interquartile ranges (IQR). Pearson's chi-square test was used to analyze differences between categorical parameters. Since most of the electrophysiological data were non-parametric, the Mann-Whitney U and Wilcoxon signed-rank tests were used for group comparisons, and Spearman's rank correlation test was applied for correlation analysis. A p-value of less than 0.05 was considered indicative of statistical significance.

3. Results

Among the 52 patients referred to our clinic with a preliminary diagnosis of sciatic neuropathy, 41 (33 male, 8 female) were included in the study. Eleven patients were excluded: six due to evidence of peripheral neuropathy and five based on radiological or electrodiagnostic findings suggestive of lumbosacral radiculopathy.

Table 1

Etiologies of sciatic neuropathy

Etiology	Number of patients (%)
Pelvic or hip surgery	13 (31.7%)
Gluteal intramuscular injection	10 (24.3%)
Gunshot wound	8 (19.5%)
Penetrating trauma	4 (9.7%)
Trauma from earthquake debris entrapment	4 (9.7%)
Malignancy	1 (2.4%)
Piriformis hematoma	1 (2.4%)

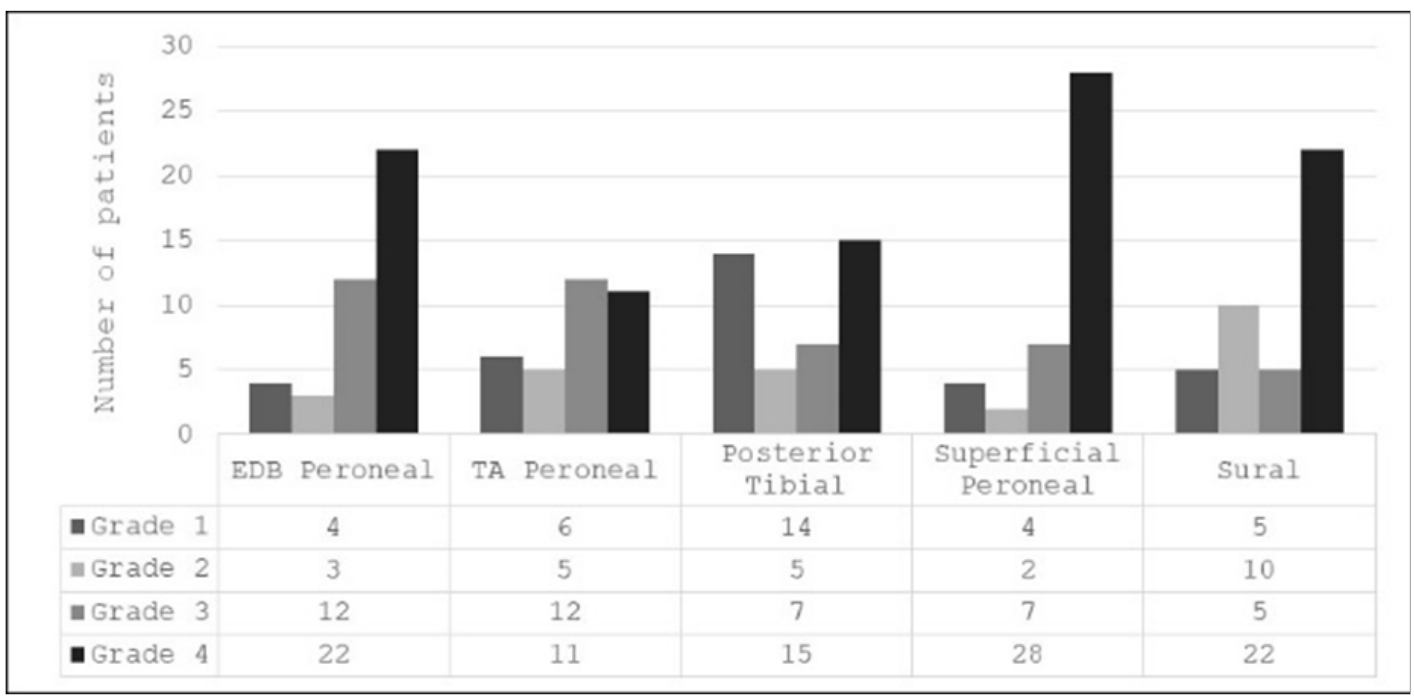
Table 2

Neurological examination findings in sciatic neuropathy patients

Sensory deficits	Number of patients (%)
Posterolateral leg	30 (73.1%)
Dorsum of the foot/lateral leg	28 (68.2%)
The sole of the foot	27 (65.8%)
Motor deficits	**Number of patients (%)**
Dorsiflexion/eversion of the foot	33 (80.4%)
Plantar flexion/inversion of the foot	27 (65.8%)
Knee flexion	14 (34.1%)

Figure 1

Grading of CMAP/SNAP amplitudes in the evaluated nerves (EDB: Extensor digitorum brevis, TA: Tibialis anterior, CMAP: Compound muscle action potential, SNAP: Sensory nerve action potential)



The mean age was 35.2 ± 14.9 years (range: 17–63 years), and the mean body mass index (BMI) was 23.2 ± 3.7 kg/m^2 (range: 17.7–31.6 kg/m^2). The time interval between injury and the electrodiagnostic study averaged 24.4 ± 35.9 months (range: 1-144 month). The etiologies of sciatic neuropathy are summarized in Table 1.

The most common sensory deficit was at the posterolateral leg within the sural nerve innervation area (73.1%), while the most frequent weakness was foot dorsiflexion or eversion (80.4%). Neurological examination findings are summarized in Table 2. The most frequent NCS abnormalities were found in the EDB-recorded peroneal nerve (90.2%) and the superficial peroneal nerve (90.2%). Abnormality rates and mean values of CMAP and SNAP amplitudes of assessed nerves are detailed in Table 3. Wilcoxon signed-rank test indicated that CMAP amplitude grading of the peroneal nerve recorded from the EDB was significantly higher than the peroneal nerve recorded from the TA [median (IQR): 4(1) vs. 3(2), p = 0.012], as well as the posterior tibial nerve [median (IQR): 4(1) vs. 3(3), p = 0.12]. Figure 1 illustrates the gradings of the evaluated nerves.

The tibialis anterior, medial gastrocnemius, and peroneus longus muscles were evaluated in all 41 patients, while the short and long heads of the biceps femoris were assessed in 33 and 27 patients, respectively. Table 4 summarizes the rate of neurogenic signs (acute or chronic) detected in the needle EMG.

The median (IQR) LEFS and DN4 scores were 29(25.3) (range: 8–75) and 8(2) (range: 2–10), respectively. According to the DN4 scale, 39 patients (95.1%) exhibited neuropathic pain. Since LEFS and DN4 scores did not have a normal distribution, non-parametric tests were employed.

Table 3

The number of abnormalities and the median (IQR) CMAP/SNAP amplitudes for the evaluated nerves.

Motor Nerves (number of patients)	Number of abnormal measurements (%)	CMAP (mV) median (IQR)
EDB recorded peroneal nerve (41)	37 (90.2%)	-*
TA recorded peroneal nerve (29)	29 (70.7%)	1.5 (5.6)
AHB recorded posterior tibial nerve (41)	27 (67.9%)	6.3 (16)
Sensory Nerves (number of patients)	**Number of abnormal measurements (%)**	**SNAP (μV)**
Superficial peroneal nerve (41)	37 (90.2)	-*
Sural nerve (41)	36 (87.8)	-*

**The CMAP of the peroneal nerve recorded from the EDB and the SNAPs of the sural and superficial peroneal nerves could not be obtained in most cases, resulting in a median value of zero. (AHB: Abductor hallucis brevis, CMAP: Compound muscle action potential, EDB: Extensor digitorum brevis, IQR: Interquartile range, SNAP: Sensory nerve action potential, SD: Standart deviation, TA: Tibialis anterior, mV: Millivolt, μV: Microvolt)*

Table 4

Frequency of acute or chronic neurogenic signs in needle electromyography

Muscle (number of patients)	Acute or chronic neurogenic findings (%)
Tibialis Anterior (41)	34 (82.9%)
Peroneus Longus (41)	32 (78%)
Medial gastrocnemius (41)	27 (65.9%)
Short head of biceps femoris (33)	22 (66.7%)
Long head of biceps femoris (27)	14 (51.9)

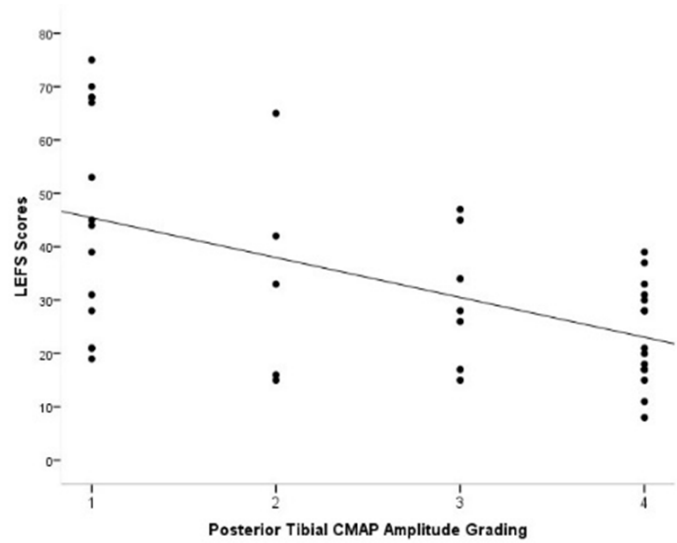
No significant effects of etiology or neurological examination findings were observed on LEFS and DN4 scores or the presence of neuropathic pain ($p > 0.05$). However, the Mann-Whitney U test indicated that the difference in LEFS scores between patients with and without weakness in plantar flexion or inversion nearly reached statistical significance [median (IQR): 26(16) vs 42(42), $p = 0.053$].

Nerve conduction study findings indicated that patients with abnormal posterior tibial CMAP had significantly lower LEFS scores [median (IQR): 26(17) vs. 44.5(41.8), $p = 0.03$]. Also, sural nerve SNAP abnormalities were associated with higher DN4 scores [median (IQR): 10(1.5) vs.8(2), $p = 0.07$]. Needle EMG evaluations revealed that neurogenic involvement in the peroneus longus and short head of the biceps femoris muscles are related to lower LEFS scores [median (IQR): 26(20) vs 65(37.5), $p = 0.001$ and 21(19.5) vs. 42(40), $p = 0.026$, respectively]. Additionally, significantly higher DN4 scores [median (IQR): 8(2) vs. 7(2), $p = 0.016$] were found when there were neurogenic findings in the needle EMG evaluation of the short head of the biceps femoris muscle.

Correlation analysis revealed a positive correlation between LEFS scores and both posterior tibial CMAP amplitude (Spearman rho: 0.52, $p < 0.001$) and peroneal CMAP amplitude recorded from the EDB (Spearman rho: 0.32, $p = 0.04$). There was also a negative correlation between LEFS scores and posterior tibial CMAP amplitude grading (Spearman rho: -0.49, $p = 0.001$), as shown in Figure 2.

Figure 2

Illustration of the negative correlation between LEFS scores and posterior tibial nerve CMAP amplitude grading



LEFS: Lower extremity functional scale, CMAP: Compound muscle action potential

4. Discussion

This study demonstrates that sciatic neuropathy significantly impairs lower extremity functions, as assessed by the LEFS. Moreover, as a novel finding, various electrophysiological parameters were found to have a significant association with the extent of functional impairment in the lower extremities.

Among the 52 cases meeting the inclusion criteria, 11 were excluded due to the presence of exclusion criteria. These patients exhibited findings indicative of either widespread peripheral neuropathy or lumbosacral radiculopathy coexisting with sciatic neuropathy. Since these conditions could independently affect LEFS scores and potentially confound NCS and needle EMG findings associated with sciatic nerve injury, they were excluded from the study.

The electrophysiological findings in patients with sciatic neuropathy were consistent with those reported in previous studies, showing varying degrees of involvement across all branches, with the peroneal nerve being the most commonly affected.[2–4,16] The LEFS scores highlight the significant impact of sciatic neuropathy on lower extremity function in nearly all cases. No significant associations were identified between LEFS and DN4 scores and demographic characteristics, etiology of sciatic nerve injury, duration since injury, or neurological examination findings. However, a near-significant statistical association was observed between lower LEFS scores and weakness in plantar flexion or inversion, which are functions performed by muscles innervated by the posterior tibial nerve.[17]

Abnormal posterior tibial CMAP in NCS and neurogenic findings in the needle EMG evaluation of the peroneus longus and the short head of the biceps femoris muscles were associated with lower LEFS

scores. Correlation analyses further confirmed the relationship between LEFS scores and posterior tibial and peroneal CMAP amplitudes. These results suggest that electrophysiological evidence of damage in both motor branches of the sciatic nerve, particularly the posterior tibial branch, significantly impacts LEFS scores.

Most of the questions in the LEFS are designed to assess the effort-intensive functions of the lower extremities.[18] Given that the posterior tibial nerve innervates several muscles—such as the long head of the biceps femoris, gastrocnemius, and soleus—responsible for high-effort movements of the thigh and posterior leg compartment, its functional integrity is crucial. Therefore, damage to this nerve understandably results in more pronounced impairments on the LEFS.[17] Furthermore, the only neurological examination finding with a potential impact on the LEFS was weakness in plantar flexion or inversion, which are functions of these muscle groups.

Interestingly, while the presence of needle EMG abnormalities in muscles innervated by the posterior tibial nerve does not independently affect LEFS scores, neurogenic findings in the peroneus longus and short head of the biceps femoris muscles do have an independent impact on LEFS. Several factors may explain this finding. First, the short head of the biceps femoris was not evaluated in the needle EMG for all cases, which may result in insufficient analysis. Additionally, considering that the peroneal branch of the sciatic nerve is frequently affected (>90%), a limited number of cases remained for intergroup comparison, which could introduce statistical bias. Lastly, a muscle's functional capacity or strength is more closely tied to recruitment patterns than to the presence of acute or chronic neurogenic changes on needle EMG.[19,20] Given these considerations, it can be inferred that NCS abnormalities in the peroneal and posterior tibial nerves are more reliable indicators of functional impairment than neurogenic findings observed in needle EMG studies in SN patients.[21]

Another noteworthy finding is that while the CMAP recorded from the peroneal nerve at the EDB exhibited a significant relationship with LEFS, no association was observed with the TA-recorded peroneal nerve. This discrepancy may be attributed to the less pronounced injury to the nerve fibers innervating the TA muscle, possibly related to the fascicular organization of the sciatic nerve.[22] The abnormality rate in the TA-recorded peroneal nerve CMAP was 70.7%, compared to 90.2% in the EDB-recorded cases. Additionally, comparing the CMAP amplitude grading of these two nerves revealed more severe involvement in the EDB-recorded peroneal nerve. Considering that the peroneal nerve's function appears to have a less pronounced impact on LEFS than the posterior tibial nerve, it can be concluded that the relatively lower degree of involvement in the TA muscle likely accounts for its lack of independent effect on LEFS.

Finally, the DN4 scale indicates that neuropathic pain is commonly observed in SN patients, with a prevalence of 95.1%. The association between sural nerve SNAP abnormalities and neuropathic pain has been demonstrated in a previous study.[6] However, detecting abnormalities in the biceps femoris's short head through needle EMG constitutes a novel finding in this study. The short head of the biceps femoris is innervated by the main trunk of the sciatic nerve, and thus, damage to this muscle may reflect more extensive injury at the proximal levels of the sciatic nerve, potentially leading to broader sensory innervation impairment and more severe neuropathic pain.[1,17]

This study has several limitations. Firstly, the cases were evaluated at a single time point. Therefore, the temporal effects of electrophysiological findings on LEFS could not be assessed. Secondly, there is a broad time interval since the onset of the SN. Some patients were assessed during the acute phase, while others were in the chronic phase, and thus, electrophysiological findings could not be evaluated independently of the nerve regeneration process. Finally, a significant proportion of patients had sciatic neuropathy caused by physical trauma (such as fractures, penetrating injuries, or traffic accidents), which also resulted in damage to muscles, joints, or bones. So, it should be considered that these injuries may have been a confounding factor in some cases, in addition to sciatic neuropathy.

5. Conclusion

This study demonstrates a significant relationship between specific electrophysiological findings and lower extremity functions in patients with sciatic neuropathy for the first time in the literature. LEFS was significantly correlated with the CMAP amplitude of the posterior tibial nerve and less so with the EDB-recorded peroneal nerve. These findings could allow for a more objective assessment of functional loss in the lower extremities of SN patients. Therefore, large-scale, prospective studies must validate these results and investigate the effects of changing electrophysiological findings over time.

Statement of ethics

Adana City Training and Research Hospital Ethics Committee approved the study with decision number 4-118 dated 15.08.2024

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers

Author contributions

HCA, SBŞ: conceptualization, methodology, investigation, and writing – original draft. HCA, SBŞ, ÖK, HF: resources, formal analysis, and writing – review and editing. HCA, HF: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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Evaluation of the Effects of Cancer Diagnosis on Smoking Behavior in Cancer Patients and Their Relatives

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Abstract

Aim: Smoking plays a role in the development of many diseases, such as atherosclerotic cardiovascular diseases, COPD, and cancer. We aimed to examine the smoking behaviors of patients and their relatives who are followed up and treated after cancer diagnosis and to identify associated factors.

Methods: Between August 2012 and January 2013, 211 patients and 208 relatives of patients admitted to the medical oncology department of Ankara University Faculty of Medicine were included. A survey of 25 questions was applied to patients and 24 to their relatives. The Beck Depression Inventory was added to the last part of the questionnaire in both groups. Three months after the completion of the forms, the participants were called again, and their smoking behaviors were questioned again.

Results: Pre-diagnosis smoking prevalence was higher among patients than their relatives (62.6% vs. 45.7%). Patients started smoking at an earlier age, and their daily cigarette consumption was significantly higher. The amount of cigarettes smoked per day increased significantly as the age of initiation decreased in both groups. The rate of smoking cessation/reduction was significantly higher in patients than in relatives (97.2% vs. 26.6%). Physicians were significantly more likely to recommend smoking cessation to patients than relatives (41.9% vs. 20%). Beck depression scores were significantly higher in patients and singles than in relatives and married patients. No significant difference was found between smoking attitude and depression scores.

Conclusions: Smoking is one of the most important preventable factors that threaten human health. It is imperative to develop effective strategies in the fight against smoking rapidly. Physicians' recommendations for smoking cessation are as effective as many other methods. After cancer diagnosis, both patients and their relatives showed a tendency to quit or reduce smoking, with patients being significantly more likely.

Keywords: *Cancer patients; smoking cessation; relatives of cancer patients; depression*

1. Introduction

Tobacco and tobacco products, especially cigarettes, are widely used in the world and our country. According to the 2020 data from the World Health Organization (WHO), the rate of tobacco and tobacco product use is 22.3%, and according to the 2022 data from the Turkish Statistical Institute (TÜİK), it is 28.3% in Turkey. While the prevalence of tobacco use is decreasing in developed countries due to public awareness and legal measures taken, it is still increasing in developing countries. As in these countries, smoking is a severe problem in our country. [1-2.] Today, smoking appears to be one of the most important health problems, leading to many diseases, especially cancer and premature deaths.

WHO has reported that smoking causes the death of five million people annually, and this number is expected to double in the next 20 years. The three main causes of smoking-related mortality are atherosclerotic cardiovascular diseases, chronic obstructive pulmonary disease (COPD) and lung cancer.[1] The relationship between smoking and cancer has been known for a long time. It has been shown that there are more than 4000 carcinogenic substances and that they harm not only the smoker but also those exposed to smoke.[3-4] Approximately 43 carcinogenic compounds have been described.[5-7] In particular, the risk of lung cancer increases 10-20 times with smoking.[8] Smoking has been found to be associated with many cancers, including not only lung cancer but also head and neck, bladder, stomach and esophageal cancer. Its relationship with breast, colon, and similar cancers is also being investigated. (Table-1)

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Table 1

Uses of some substances found in cigarettes (9).

Arsenic	Poison manufacturing
Methanol	In rocket gas production
DDT	In the production of insecticides
Carbon Monoxide	Present in the exhaust gas
Cadmium	Available in vehicle accumulators
Hydrogen cyanide	In the gas chambers
Butane gas	Cylinder and lighter gas
Acetone	Nail polish and chemical remover
Naphthalene	Moth spraying
Ammonia	Chemical cleaning works

Among cancer prevention policies, smoking has been shown to be the most important preventable cause of approximately 21% of cancer deaths worldwide.[2] The most important measure to be taken to reduce lung cancer cases is to reduce smoking in the community. In developed countries where anti-smoking policies are implemented, and smoking is reduced, it has been found that the incidence and mortality rates of smoking-related diseases have gradually decreased over the years.[2,9-11] Most smokers know the association of smoking with cancer and premature mortality. Despite this, many people continue to smoke. The difficulty in perception explains this behavior due to the fact that the severe threat does not appear immediately and cannot be observed concretely. In addition, the strong addictive effect of nicotine makes it difficult to quit smoking. According to many studies, a close relationship has been found between smoking and depression.[12-13]

Important data have been obtained on the effectiveness and responsibility of physicians in smoking cessation studies. According to the literature, only 5% of people quit smoking with a physician's recommendation. Repeated treatments are recommended until permanent cessation is achieved. In the world and our country, in recent years, some decrease in the number of smokers has been achieved with public education and legal measures limiting smoking areas.[14-15]

Table 2

The relationship between smoking and cancer (18)

Cancers with a proven etiological relationship with smoking	Cancers suspected to be related to smoking
Lung cancer	Breast cancer
Head and neck cancers	Basal cell cancer
Esophageal cancer	Squamous cell carcinoma of the skin
Mesothelioma	
Colorectal cancer	
Renal pelvis, ureter, bladder cancer	
Pancreatic cancer	
Myeloid leukemia	
Penile cancer	
Cervix cancer	
Stomach cancer	

Patients diagnosed with cancer and undergoing treatment are advised to quit smoking, regardless of whether it is related to smoking or not. In addition to reducing additional morbidities, smoking cessation has also contributed positively to survival in some studies. Smoking cessation prolongs survival in patients with small cell lung cancer undergoing thoracic radiotherapy and in operated early-stage non-small cell lung cancer. There is strong data that smoking cessation increases survival.[16] Approximately 50% of smokers will die from tobacco-related diseases, and smokers will lose approximately 13 years of their lives because of this habit.[1,17-18] (Table-2)

Physicians who carry out the follow-up and treatment of patients with cancer have responsibilities for smoking cessation for these patients and their relatives. Obtaining information about the smoking attitudes of these patients and their relatives will guide physicians in the fight against smoking. In this study, the smoking behavior of patients and their relatives followed at Ankara University Faculty of Medicine, Department of Medical Oncology, and the situation that occurred after the diagnosis of cancer were analyzed. In this study, which was designed as a questionnaire, it was planned to learn the demographic determinants for example income level, education and place of residence and to determine the relationship between them and smoking behavior. In addition, the informing behaviors of healthcare workers about smoking were also questioned in the questionnaires.

In the PSYCOG (Psychosocial Collaborative Oncology Group) study conducted by Derogatis et al., 47% of cancer patients were reported to have a diagnosable mental disorder. This rate is around 20-40% in cancer and non-cancer patients.[19] Many people associate smoking with stress and state that they smoke to relax. Considering that the situation may be similar for oncology patients, it was planned to define this situation scientifically with the Beck Depression Inventory in the last part of the study. The depression score of the participants was calculated, and it was aimed to evaluate the relationship between these scores and smoking behavior and demographic data.

2. Materials and Methods

Patients and their relatives who applied to Ankara University Faculty of Medicine, Department of Medical Oncology between August 2012 and January 2013 and whose follow-up and treatment continued in the clinic or outpatient clinic were included in this study. Questionnaires regarding demographic data and smoking behavior were administered to patients and their relatives. Beck depression test was performed on patients and their relatives to screen for depression. Participants whose health status or education level was not suitable were read the questions in the questionnaire forms. Three months after the completion of the forms, the participants were called again, and their smoking attitudes were questioned again. In addition, comorbidities and medications used by the participants were questioned. According to the oncologic disease stage, participants were grouped as metastatic and non-metastatic.

2.1. Statistical Analysis

The data obtained in the study were analyzed with the SPSS-15 program. Statistics were expressed as mean ± standard deviation for variables with normal distribution, median value (min-max) for variables with non-normal distribution, number of cases and (%) for nominal variables. The significance of the difference in terms of means between two groups was analyzed by t-test, and the significance of the difference in terms of medians between groups was analyzed by Mann-Whitney U-test. In cases where there were more than two groups, the difference in means between the groups was evaluated with the ANOVA analysis of variance test, and the significance of the difference in terms of median values was evaluated with the Kruskal-Wallis test. For nominal variables, Pearson's Chi-Square or Fisher's exact test was used. Results were

considered statistically significant at p<0.05. Ethics committee approval for our study was received on June 24, 2013, number 10-416-13.

3. Results

A total of 208 relatives (112 male and 96 female) and 211 patients (123 male and 88 female) were included in the study. The characteristics of patients and relatives are summarized in Table 3. The majority of the patients included in the study were primary school graduates, with a rate of 44.1%, while 34.1% of the relatives were primary school graduates and 33.2% were university graduates. 6.6% of the patients and 2.4% of the relatives were illiterate. The majority of the working population in both groups were civil servants. The majority of patients and their relatives lived in metropolitan areas, and in both groups, married patients were more common than single patients. The majority of patient relatives were spouses, followed by children. The characteristics of patients and their relatives were similar except for age and gender. The relatives were younger than the patients, and the majority of them were women. (Table-3)

Table 3

Demographic characteristics of patients and relatives

	Patient	Patient relatives
Gender		
• Woman	88	112
• Male	123	96
Median Age	57 (19-89)	43 (18-80)
Marital Status		
• Married	%82,9	%79,7
• Single	%17,1	%20,3
Education Status		
• Literate	%15,2	%6,7
• Primary - high school	%66,8	%60,1
• University	%18	%33,2
Job Status		
• Employee	%48,6	%49,8
• Not working	%51,4	%50,2
Place of Residence		
• Village-town	%26,2	%21,8
• Province - metropolitan	%73,8	%78,2
Total Number of Participants	211	208

In the study, malignancies were divided into two groups: smoking-related malignancies and malignancies that were less or not associated with smoking. Smoking-related malignancies included lung, head and neck, stomach, esophageal and bladder cancers. Other malignancies were considered as the second group. In terms of malignancy, 42.6% of the patients had cancer closely related to smoking. 45.9% of the patients were in the metastatic stage.

37.4% of patients and 54.3% of relatives had never smoked (p<0.001). Pre-diagnosis smoking prevalence was found to be significantly higher among patients than among their relatives. Among the non-smokers, 87.3% had second-group malignancies that were not grouped as smoking-related. Of these, only 12.7% had one of the smoking-related cancers. Table 4 shows the daily cigarette consumption of the patients and their relatives before the diagnosis. When the amount of cigarettes consumed per day is analyzed, the amount of cigarettes consumed per day is higher in patients than in their relatives. Patients and relatives accounted for 80.4% and 71.0% of those with 21-30 or >30 cigarettes per day, respectively (p<0.001). The daily cigarette consumption of patients was found to be significantly higher than that of their relatives. (Table-4)

Table 4

Number of cigarettes smoked before diagnosis

Number of cigarettes	Patient	Patient relatives
1-5	%10.1	%17,2
6-10	%10.1	%16,1
11-20	%34.1	%47.3
21-30	%28.7	%9.7
>30	%17.0	%9,7

The age at initiation of smoking in patients and relatives was as follows: The median age at initiation of smoking was 15.0 in patients and 18.0 in relatives (p:0.002). Significantly, patients started smoking at an earlier age than their relatives. As the age at initiation of smoking decreased, the number of cigarettes smoked per day increased. While the median age at initiation was 15 years for those who smoked more than 30 cigarettes per day, the median age at initiation was 18 years for those who smoked 1-5 cigarettes per day (p:0.021). Similarly, the group with the highest daily cigarette consumption had the youngest age at initiation, and the median age was 16 years (p:0.076). Among the patients, 79.7% of never-smokers were women. Among the relatives of the patients, 73.2% of never-smokers were women (p<0.05). Smoking among women was found to be significantly less in both groups. When educational status and smoking habits were compared, the primary school-high school group constituted the majority of never-smokers (54.4%) (p<0.001).

Similarly, the highest proportion of never-smokers was found in the primary school-high school group (64.6%) (p:0.035). When patients and relatives were asked why they smoked, 48.8% and 43.2% of both groups stated that they smoked out of habit. The rate of those who thought that they did not suffer any harm was 4.1% in patients and 6.8% in relatives. When smoking behavior was examined according to income level, the rate of never smoking increased as the income level decreased in patients (55.1%). Similarly, in relatives, the group with the lowest income level had the highest rate of never smoking (39.8%).

After the diagnosis of malignancy, 31.3% of the patients showed a change in attitude towards reducing the number of cigarettes smoked per day or quitting smoking completely. The rate of those who continued smoking in the same way was 2.4%. After the diagnosis, 97.2% of the patients showed a positive behavior model in smoking. Among relatives of patients who smoked, 26.6% were positively influenced to reduce or quit smoking after diagnosis. Of these, 64.9% did not change their smoking behavior (p<0.001). The rate of smoking cessation and reduction was found to be significantly higher among patients than among their relatives. Smoking cessation rates were 80.3% in patients with smoking-related malignancies, compared to 40% in patients with other malignancies. Among current smokers, 78.9% had non-smoking-related malignancies (p<0.001). The rate of smoking cessation and reduction was significantly higher in patients with smoking-related cancer than in patients with other malignancies.

Among the relatives of patients who reduced or quit smoking,

70.5% were relatives of patients with other malignancies not grouped as smoking-related. The remaining 29.5% were relatives of patients with smoking-related malignancies. When the patients were asked whether smoking played a role in their disease, 60% of them answered yes. When asked whether your disease affected your smoking cessation, 45.7% answered yes. When the relationship between smoking cessation and age was analyzed, the median age of those who had reduced/quit smoking was 58 and 50, respectively, for those who still smoked. When the median age was compared, the difference was statistically significant (p:0.029). The tendency to reduce/stop smoking was significantly higher in older patients. When the smoking reduction/cessation rates of patients with metastatic disease and those with non-metastatic stage were compared, 81.8% of metastatic patients and 85.9% of non-metastatic patients reduced/quit smoking. The rate of smoking reduction/cessation was 57.1% in the relatives of metastatic patients and 42.9% in the non-metastatic group (p:0.011). Relatives of metastatic patients were significantly more likely to reduce/quit smoking than non-metastatic patients.

When patients and their relatives were asked whether their physicians recommended them to quit smoking, 41.9% of the patients stated that they were recommended. This rate was found to be 20% in relatives (p:0.001). It was understood that physicians made suggestions about smoking significantly more to patients than to their relatives. The rate of those who received support from smoking cessation outpatient clinics was 7.4% in the patient relatives group and 8.8% in the patients. When their opinions on legal regulations regarding the consumption of tobacco and tobacco products were taken, 38.3% of patients and 48.5% of relatives reported that they were affected by the ban on smoking in closed areas. Three months after the survey, patients and their relatives were called by telephone to re-interrogate smoking behavior. Some patients and relatives could not be reached for various reasons (exitus, wrong phone number, etc.). Of the patients and relatives who could be reached, 10% of those who still smoked had quit smoking after the survey. 7% had reduced the number of cigarettes per day after the survey.

The grouping in the Beck Depression Inventory, which was used in our study and validated in our country, is defined in Table 5.

Table 5

Beck Depression Inventory

Score	Evaluation
<10	Normal
11-16	Mild mood disturbance
17-24	Borderline clinical depression
>24	Depression

The mean Beck Depression Inventory score of patients was 12.79±9.039 (minimum 0-maximum 49 points). The mean score of relatives was 9.20±7.371 (minimum 0-maximum 38 points). While 10.2% of the patients had a depression score >24, this rate was 3.4% among the relatives. When the depression scores of relatives and patients were analyzed, it was found that the majority of those with borderline clinical depression or depression were patients. (66.1% and 75.0%). The majority of the group with mild mood disturbance or considered normal was composed of patients' relatives (53.1% and 55.7%) (p: 0.001). Depression scores were significantly higher in patients than in their relatives.

When depression and smoking status were compared, 66.7% of the patients in the group with the highest depression score were smokers who quit smoking. Similarly, 53.1% of those in the group with the lowest depression score were smokers who quit smoking. The majority of those who quit smoking (47.3%) were in the group with the lowest depression score. When the group with the highest depression score was analyzed, the highest percentage was composed of smokers who quit smoking (12.7%) (p=0.564). There was no significant relationship between smoking behavior and depression. When depression was compared with smoking status in relatives, 57.1% of those with the highest depression score were never smokers.

Similarly, 56.9% of those with the lowest depression score were never smokers. The majority of those who quit smoking (65.9%) were in the group with the lowest depression score. In the group with the highest depression score, the highest percentage was still smoking (6.0%) (p=0.210). Similarly, there was no significant relationship between smoking behavior and depression among the relatives of the patients. When the rate of depression was analyzed according to the marital status of the patients, single patients had significantly higher depression scores than married patients (p:0.0447). Similarly, the depression scores of single patients' relatives were higher than those of married patients (p: 0.042). Depression scores were significantly higher in single patients compared to married patients.

4. Discussion

In this study, a cross-sectional evaluation of a limited number of patients and their relatives who are being followed up and treated in the Department of Medical Oncology, Ankara University Faculty of Medicine was made. Therefore, the study has some limitations related to the quantity and quality of participants.

In our study, it was found that patients' relatives were younger, and the female gender was predominant in the demographic data of patients and their relatives, which has also been found in other studies.[20] Pre-diagnosis smoking frequency was found to be significantly higher among patients than among their relatives. Smoking-related cancers were also less common in non-smokers among patients. In addition, the daily cigarette consumption of patients was significantly higher than that of their relatives. In addition, patients initiated smoking at a significantly earlier age than their relatives. As the age of initiating smoking decreased in patients and relatives, the amount of cigarettes smoked per day increased. A significant relationship was shown between these two parameters. This is an expected finding that was among the hypotheses of the study. In a study conducted in Turkey, it was shown that the earlier the age at initiation of smoking, the more likely it is to continue smoking in adulthood.[21] The findings in the literature support these findings. Women are significantly less likely to smoke among patients and their relatives, but the rate tends to increase gradually.[22] Among patients and their relatives, smoking was found to be significantly lower in those with primary and high school education. This finding may be explained by the high number of participants at the primary and high school levels when categorized according to education.

The rate of smoking cessation and reduction was significantly higher among patients than among their relatives. This difference was particularly pronounced in patients with smoking-related cancer. The tendency to reduce/quit smoking was significantly higher in older patients. Relatives of non-metastatic patients were significantly more likely to reduce/quit smoking than metastatic patients. A study in the literature made a partially similar assessment. In a study conducted in the USA, it was found that relatives of patients with lung cancer had higher smoking cessation

rates than relatives of patients with colorectal cancer.

Similarly, in our study, it was shown that patients with smoking-related malignancies quit smoking at a higher rate. As expected, the tendency to reduce/quit smoking is predominant in patients who face a life-threatening situation such as cancer diagnosis and treatment. After diagnosis, patients with cancer show more interest in healthy living recommendations than normal individuals. Physicians and the media are effective in this regard. The positive effect of a smoke-free life on the success and risks of treatment and prognosis is emphasized a lot. Interestingly, relatives of patients who are in close relationship with the patient with cancer and who participate in the process exhibit less smoking reduction/cessation behavior.[20]

In a study conducted in Belgium, 70 NSCLC patients underwent quality of life questionnaire preop and postop at 1-3-6-12 months and were questioned about their smoking behavior and symptoms. Except for never-smokers, all patients who still smoked, those who quit after the disease and those who quit before the disease complained of fatigue. Dyspnea in the first six months was significantly less in the group that quit smoking. Those who continued to smoke could not reach their preop physical performance in the postop period, and persistent dyspnea and chest pain were more common. Symptomatic questioning was not performed in our study. In a study conducted on patients with head and neck squamous cell carcinoma, when the smoking cessation behaviors of patients who received surgical treatment, chemotherapy, radiotherapy and/or combined treatment were examined, smoking cessation rates were higher in patients who received surgical treatment alone or in combination with other treatments (p:0.004).[24]

Physicians have important duties and serious responsibilities in the fight against smoking. In this study, approximately 42% of patients with cancer reported that their physicians made suggestions about smoking. The rate of patients quitting smoking with the recommendations of physicians is 5-10%. Considering the number of patients seen by these physicians, this rate exceeds the smoking cessation outpatient clinics in terms of impact power. In the study, the application to these outpatient clinics, which are active and well-publicized in our hospital, was low. Physicians who see cancer patients significantly make their recommendations on smoking to patients rather than their relatives. However, the physician bears the same responsibility for the relatives of the patients. Moreover, this measure is an effective preventive medicine approach when there is no smoking-related severe disease yet. It is very important to include attitude education effectively in medical education for the fight against smoking.[9-11,23]

Depression scores were significantly higher in patients than in their relatives. In the PSYCOG study conducted by Derogatis et al., 47% of cancer patients were reported to have a diagnosable mental disorder. This rate is around 20-40% in cancer and non-cancer patients.[19] Depression scores were found to be significantly higher in single patients compared to married patients. No significant difference was found between smoking behavior and depression scores in patients and their relatives. The reasons for this may be various. The Beck Depression Inventory is not an essential approach for the diagnosis of depression; it can only provide rough information. Since a few questions in the Beck Depression Inventory were related to the performance status of the patients, it was not an ideal questionnaire for the relatives of the patients. We chose to use the same scale for standardization in the study. In our study, the rate of smokers increased as the depression score increased, but the difference was not statistically significant. The small number of participants may have affected the statistical difference.

Statement of ethics

Ankara University Faculty of Medicine Ethics Committee approved the study with June 24, 2013, number 10-416-13.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers Thesis number: 455789, https://tez.yok.gov.tr/UlusalTezMerkezi/

Author contributions

ZK, FCS: conceptualization, methodology, investigation, and writing – original draft. ZK, FCS: resources, formal analysis, and writing – review and editing. ZK, FCS: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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The Role of the Nine-Hole Peg Test and Neurophysiological Tests in the Classification of Carpal Tunnel Syndrome

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Abstract

Aim: The aim of this study was to investigate the effectiveness of the use of the nine-hole nail test and neurophysiological tests in the diagnosis and classification of carpal tunnel syndrome (CTS).

Methods: This study was planned as a prospective cross-sectional study. Age, gender, occupation, height (cm), weight (kg), body mass index (BMI-kg/m2) values of all patients included in the study were recorded. In addition to the nine-hole nail test, LANNS, DN4 model was applied to CTS patients. In addition, the duration of the patients' complaints (months), the classification of their clinical findings and electrophysiological staging were recorded. The sensory and muscle strength examination of the hand was evaluated with Phalen and Tinel tests. Nerve conduction study (NCS) was performed with Cadwell Sierra EMG in our Neurophysiology Laboratory and normal values from our Clinical Neurophysiology Laboratory were used.

Results: A positive (linear) moderate correlation was found between the BCTQ FSS value and the left nine-hole nail test, the defective nine-hole nail test, the BCTQ SSS, LANNS and DN 4 values (r=0.387; r=0.350; r=0.649; r=0.431; r=0.490, respectively). A positive (linear) moderate correlation was found between the LANNS value and the defective nine-hole wooden nail test and DN 4 values (r=0.395; r=0.666, respectively). A positive (linear) moderate correlation was found between the DN 4 value and the BCTQ SSS, the BCTQ FSS and LANNS values (r=0.599; r=0.490; r=0.666, respectively).

Conclusions: It is possible to say that the nine-hole nail test and BCTQ tests are effective and reliable tools in the clinical and functional evaluation of CTS.

Keywords: *Carpal tunnel syndrome; electrophysiology; BCTQ; Nine-hole nail test*

1. Introduction

Carpal tunnel syndrome (CTS) is characterized by compression of the median nerve within the carpal tunnel in the wrist. CTS is typically characterised by symptoms of pain, numbness, tingling and weakness in the hand and fingers. Sensory symptoms may include nocturnal pain that can radiate from the hand into the forearm, elbow and shoulder, and paresthesia or hypoesthesia in the areas innervated by the median nerve. Motor symptoms include clumsiness, weakness in the hand and fingers, and interference with daily activities[1,2]. The diagnosis of CTS is based on clinical assessment, neurophysiological testing and imaging.

Neurophysiological testing, which measures nerve conduction velocities, is also an important tool in assessing the severity of the disease[3].

The nine-hole peg test is a simple but effective technique used in the diagnosis of CTS. This test assesses motor function based on the movement of the fingers and hands. In the early stages of CTS, neurophysiological testing provides more accurate results, while the nine-hole peg test is a simpler and quicker alternative[4]. However, studies comparing these two tests are limited.

Our aim in this study is to compare the nine-hole peg test and neurophysiological tests in carpal tunnel syndrome.

2. Materials and Methods

2.1. Study design and data collection

The present study was meticulously designed as a prospective cross-sectional study. Ethical approval for the study was obtained from the Ethics Committee of Adana City Training and Research Hospital (Meeting date: 22/06/2022; Meeting number: 108;

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Decision number: 1997). Following the acquisition of ethical approval, patients were enrolled in the study from 25 July 2022 to 25 April 2023. All patients who approved informed consent were included in the study. The study was carried out in the Neurology Clinic and Neurophysiology Laboratory of Adana City Training and Research Hospital, Health Science University.

Criteria for inclusion in the study;

1. Patients over 18 years old
2. Those who approved participation in the study
3. Patients with clinical findings consistent with carpal tunnel syndrome

Criteria for exclusion in the study:

1. Those under 18 years of age
2. Those who refused participation in the study
3. Patients with polyneuropathy or neurodegenerative diseases
4. Patients with diseases causing neuropathy, such as diabetes mellitus
5. Patients who had surgery for carpal tunnel syndrome
6. Patients undergoing treatment for neuropathic pain
7. Patients with clinical or electrodiagnostic findings consistent with ulnar or radial neuropathy

Data recorded for all patients included age, gender, occupation, weight (kg), height (cm), and body mass index (BMI, kg/m^2). In addition to the Nine-Hole Peg Test (NHPT)[5], the LANNS and DN4 models were applied to patients with CTS. The duration (in months) of their complaints, clinical classification, and electrophysiological staging were also recorded.

2.2. Clinical Evaluation

The clinical findings comprised the presence of nocturnal paresthesia in the first three fingers (Flick sign), paresthesia or pain with exercise or hand movements in the first three fingers, and weakness or atrophy in the hand muscles innervated by the median nerve. The evaluation of sensory and muscle strength in the hand was conducted using the Phalen and Tinel tests. The clinical classification is outlined below:

1. Only nocturnal paresthesia
2. Diurnal and nocturnal paresthesia
3. Loss of sensory
4. Atrophy or weakness in the thenar muscles innervated by the median nerve
5. Paralysis of the thenar muscles innervated by the median nerve

2.3. Neurophysiological Evaluation

Nerve conduction studies (NCS) were performed using the Cadwell Sierra EMG device (Cadwell Laboratories, Kennewick, Washington, USA) in the Neurophysiology Laboratory. Surface electrodes were utilised for the purposes of recording and stimulation. NCS was performed when the extremities were above 32°C. In cases where the extremities were cold, they were warmed up. The filter settings for sensory and motor NCS were set to 20 Hz-2 kHz and 20 Hz-10 kHz, respectively. For the purpose of sensory NCS, sensitivity and sweep rate were set to 10 µV/division and 1 ms/division, respectively. For motor NCS, the sensitivity and sweep rate were set to 2 mV/division and 5 ms/division, respectively. Bilateral median and ulnar sensory-motor NCS were performed on all patients. It is also noteworthy that all nerves were stimulated supramaximally. The recording for median and ulnar motor NCS was obtained from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles, respectively. For the conduction of motor nerve studies, the distance between the stimulation point and the recording electrode at the wrist was set at 5 centimetres.

For median motor NCS, the stimulation sites were located at the wrist and elbow, while for ulnar motor NCS, the stimulation sites were positioned at the wrist, below the elbow, and above the elbow. In the case of median sensory NCS, antidromic recording was performed at the second finger-wrist segment, and orthodromic recordings were conducted at the second finger-wrist, palm-wrist, and wrist-elbow segments (mixed nerve). Ulnar sensory NCS was performed at the 5th finger-wrist segment using antidromic stimulation.

Neurophysiological classification was conducted in accordance with the established guidelines.

1. Mild CTS: SNCV of the median nerve at the 2nd finger-wrist segment was observed to be slowed, with a peak latency above 40.9 m/s and/or an onset latency above 44.6 m/s.
2. Moderate CTS: Slowing of sensory nerve conduction velocity (SNCV) at the 2nd finger-wrist segment and delayed distal median motor latency of more than 3.7 ms
3. Severe CTS: Absent distal median compound sensory action potential (CSAP) and delayed distal median motor latency of more than 3.7 ms
4. Very severe CTS: Absent distal median CSAP and compound muscle action potential (CMAP)

2.4. Nine Hole Peg Test Procedure

The Nine Hole Peg Test was used to demonstrate dexterity in the hand. This device is a setup consisting of a square platform and a storage box. There are 9 holes in the square area (12.7x2 cm) and 9 cylinders suitable for these holes. The diameter of the holes is 0.71 cm, the diameter of the cylinders is 0.64 cm, the length is 3.2 cm, the distance between the holes is 3.2 cm, the hole depth is 1.3 cm and the storage box size is 13x13 cm. Patients are asked to quickly take the 9 cylinders from the storage box, place them in the holes and then back in the storage box. The time is measured in seconds with a stopwatch[5].

2.5. Statistical Analysis

The statistical analysis of the data was conducted utilising SPSS (Statistical Package for the Social Sciences) version 25.0. Categorical variables were summarised as frequencies and percentages, while continuous variables were summarised as medians. The Shapiro-Wilk test was employed to ascertain the normal distribution of the parameters in the study. The chi-square test was used to compare categorical variables. For non-normally distributed parameters, the Mann-Whitney U test was applied. The relationships between continuous measurements were determined by employing the Spearman's rho correlation test. A p value below 0.05 was considered statistically significant.

3. Results

The mean age of the patients was 46.1 ± 9.7 years (median: 46 years). Five of the patients (10.9%) were male and 41 (89.1%) were female. The distribution of CTS across the body was found to be uneven, with 29 (63%) cases affecting the right side and 17 (37%) cases affecting the left side. The distribution of electrophysiological classes was as follows: 14 (30.4%) mild, 26 (56.5%) moderate, and 6 (13%) severe.

In clinical classification, 5 (10.9%) patients had only nocturnal paresthesia, 30 (65.2%) had both nocturnal and diurnal paresthesia, 10 (21.7%) had sensory loss, and 1 (2.2%) had atrophy or weakness in the thenar muscles innervated by the median nerve.

Furthermore, 20 (43.5%) patients exhibited abnormal LANNS findings, while 35 (76.1%) patients demonstrated abnormal DN4 findings (see Table 1 for details). A statistically significant difference was observed in the rate of abnormal DN4 findings, with higher incidences observed on the left side compared to the right ($p=0.004$). Furthermore, an analysis of the mean LANNS values revealed that they were higher on the left side compared to the right ($p=0.012$). No statistically significant differences were observed between the other parameters and groups ($p>0.05$) (Table 2).

Table 1

Analysis of demographic, clinical and applied tests of patients

	Number (n)	Percentage (%)
Gender		
Male	5	10.9
Female	41	89.1
Working status		
Yes	13	28.3
No	33	71.7
Side		
Right	29	63
Left	17	37
Electrophysiological classification		
Mild	14	30.4
Moderate	26	56.5
Sever	6	13.0
Clinic classification		
Only nocturnal paresthesia	5	10.9
Nocturnal and diurnal paresthesia	30	65.2
Loss of sensation	10	21.7
Atrophy or weakness of thenar muscles with median innervation	1	2.2
LANNS		
Abnormal	20	43.5
Normal	26	56.5
DN 4		
Abnormal	35	76.1
Normal	11	23.9
	Average±SD	Med (Min-Max)
Age (years)	46.1±9.7	46 (24-65)
Complaint period (months)	16.0±27.2	6 (0.25-120)
nine-hole peg test right	22.5±3.3	22.1 (17.8-31.0)
nine-hole peg test left	23.1±3.5	22.8 (18.1-38)
nine-hole peg test that is broken	23.5±3.4	23.4 (18.5-38)
Median nerve motor latency	4.75±1.3	4.34 (63.28-8.75)
Median nerve motor action potential	11.1±4.9	10.5 (2.3-24.8)
Median nerve sensory velocity	28.3±11.6	32.9 (0-38.9)
Median nerve sensory action potential	22.9±16.7	18.8 (0-73.9)
BCTQ SSS	30.9±8.2	30.5 (15-49)
BCTQ FDS	20.8±6.9	20.5 (8-34)
LANNS	12.2±4.6	11 (5-24)
DN 4	5.52±1.6	6 (2-9)

A weak positive linear correlation was identified between BCTQ SSS and Nine-Hole Peg Test (right) values (r=0.038). Moderate positive correlations were found between the impaired Nine-Hole Peg Test and BCTQ FDS, LANNS, and DN4 values (r=0.359; r=0.649; r=0.587; r=0.599).

A moderate positive correlation was identified between BCTQ FDS values and impaired Nine-Hole Peg Test values, BCTQ SSS, LANNS, and DN4 on the left side (r=0.387; r=0.350; r=0.649; r=0.431; r=0.490). A moderate positive correlation was identified between LANNS values and impaired Nine-Hole Peg Test and DN4 values (r=0.395; r=0.666). Furthermore, a moderate positive correlation was identified between DN4 values and BCTQ SSS, BCTQ FDS, and LANNS values (r=0.599; r=0.490; r=0.666) (Table 3).

4. Discussion

The findings of this study provide important insights into the clinical and electrophysiological characteristics of CTS patients and the relationships between various tests used in diagnosing the disease. The mean age of the patients and the predominance of females support the hypothesis that CTS is more prevalent in middle-aged individuals, especially women[6]. The high proportion of female patients in this study lends further support to the relationship between gender and CTS.

The electrophysiological classification results indicate that the majority of patients have moderate (56.5%) and mild (30.4%) CTS, suggesting that CTS often does not manifest prominent symptoms until it reaches the moderate stage. However, as symptoms progress, there is an attendant increase in neurophysiological impairments[7]. The clinical findings indicate that 65.2% of patients experienced both diurnal and nocturnal paresthesia, suggesting that symptoms become persistent throughout the day as the disease progresses. While the rate of atrophy or weakness in the thenar muscles due to median nerve damage was low, it is possible that this finding may become more prominent in the later stages of the disease[8].

The LANNS and DN4 tests results indicate that these tests can be valuable diagnostic tools in the assessment of CTS. Specifically, the DN4 test may offer more information about nerve damage, thus making it a useful clinical tool in evaluating CTS[9].

Table 2

Demographic, clinical and test results of the patients according to the right and left upper extremities

	Right (number=29) Percentage (%)	Left (number=17) Percentage (%)	p
Gender			
Male	3 (10.3)	2 (11.8)	0.891
Female	26 (89.7)	15 (88.2)	
Working status			
Yes	9 (31)	4 (23.5)	0.585
No	20 (69)	13 (76.5)	
Electrophysiological classification			
Mild	7 (24.1)	7 (41.2)	0.476
Moderate	18 (62.1)	8 (47.1)	
Sever	4 (13.8)	2 (11.8)	
Clinic classification			
Only nocturnal paresthesia	3 (10.3)	2 (11.8)	0.500
Nocturnal and diurnal paresthesia	17 (58.6)	13 (76.5)	
Loss of sensation	8 (27.6)	2 (11.8)	
Atrophy or weakness of thenar muscles with median innervation	1 (3.4)	-	
LANNS			
Abnormal	10 (34.5)	10 (58.8)	0.109
Normal	19 (65.5)	7 (41.2)	
DN 4			
Abnormal	18 (62.1)	17 (100)	0.004*
Normal	11 (37.9)	-	
	Average±SD	Average±SD	p
Age (years)	44.8±9.8	48.2±9.3	0.194
Complaint period (months)	14.6±24.2	18.4±32.3	0.398
Nine-hole peg test right	23.1±3.1	21.5±3.5	0.074
Nine-hole peg test left	22.4±3.1	24.2±3.9	0.148
Nine-hole peg test that is broken	23.1±3.1	24.2±3.9	0.546
Median nerve motor latency	4.87±1.4	4.56±1.2	0.432
Median nerve motor action potential	11.1±5.7	11.2±3.3	0.419
Median nerve sensory velocity	27.9±12.0	28.8±11.3	0.802
Median nerve sensory action potential	19.2±13.5	29.4±19.8	0.083
BCTQ SSS	30.3±9.3	31.8±5.9	0.419
BCTQ FDS	19.2±7.3	23.4±5.4	0.058
LANNS	10.9±4.3	14.2±4.4	0.012*
DN 4	5.27±1.8	5.94±0.7	0.156

Table 3

Results of patients' nine-hole nail test results according to BCTQ, LANNS and DN4

Parameters	BCTQ SSS		BCTQ FDS		LANNS		DN 4	
	r	p	r	p	r	p	r	p
Nine-hole peg test right	0.038*	0.022	0.125	0.407	0.256	0.085	0.084	0.579
Nine-hole peg test left	0.207	0.167	0.387**	0.008	0.167	0.269	0.101	0.503
Nine-hole peg test that is broken	0.359*	0.014	0.350*	0.017	0.395**	0.007	0.203	0.175
Median nerve motor latency	0.187	0.213	0.127	0.399	-0.027	0.858	-0.067	0.657
Median nerve motor action potential	-0.118	0.434	-0.024	0.875	0.089	0.557	-0.037	0.809
Median nerve sensory velocity	-0.255	0.087	-0.102	0.501	-0.027	0.859	-0.003	0.983
Median nerve sensory action potential	-0.154	0.307	-0.087	0.564	0.111	0.461	0.032	0.834
BCTQ SSS			0.649**	<0.001			0.599**	<0.001
BCTQ FDS	0.649**	<0.001					0.490**	0.001
LANNS	0.587**	<0.001	0.431**	0.003			0.666**	<0.001
DN 4	0.599**	<0.001	0.490**	0.001	0.666**	<0.001		

The higher rate of abnormal DN4 findings on the left side and the higher LANNS values in the left hand suggest that neurological impairments may be more pronounced on the left side, indicating possible differences between the left and right sides in terms of neurophysiological effects[10].

The present analysis sought to explore the relationship between BCTQ and the Nine-Hole Peg Test, with the objective of determining the existence of any correlation between the two tests. The results of the analysis revealed that there was a weak to moderate positive correlation between the two tests. Of particular note are the medium correlations observed between impaired Nine-Hole Peg Test results and BCTQ FDS, LANNS, and DN4. This finding suggests that combining clinical findings with electrophysiological tests may facilitate more precise classification of CTS[11]. Furthermore, stronger relationships with BCTQ SSS, FDS, and DN4 imply that these tests are essential in evaluating the impact of CTS on daily living activities. The Nine-Hole Peg Test is a simple yet effective tool for monitoring CTS in clinical settings, as its results correlate with other diagnostic tests.

This study has some limitations. These include the relatively small sample size and the reliance on data from a single healthcare centre. Furthermore, the evaluation of factors such as the patients' treatment processes and the continuity of their symptoms was not undertaken, which may limit the generalizability of the findings. Consequently, subsequent studies encompassing larger patient populations and incorporating long-term follow-up will be instrumental in substantiating the validity of these findings.

5. Conclusion

The findings of this study highlight the relationships between various tests used in the clinical and neurophysiological evaluation of CTS and their importance in disease management. The Nine-Hole Peg Test and BCTQ tests have been demonstrated to be effective and reliable tools in the clinical and functional assessment of CTS. Furthermore, neuropathic pain tests such as LANSS and DN4 have the potential to inform treatment strategies for CTS patients.

Statement of ethics

This study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee (Meeting number: 108; meeting date: 23.06.2022; decision number: 1997).

genAI

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The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers

Author contributions

EBS, ME: conceptualization, methodology, investigation, and writing – original draft. EBS, ME, ZA, HF: resources, formal analysis, and writing – review and editing. EBS, ME, SB, DO, ZA, HF: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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Evaluation of the Effect of APFEL Risk Score and Fasting Times on Postoperative Nausea and/or Vomiting

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Abstract

Aim: Postoperative nausea and vomiting (PONV) occurs in 30-80% of elective surgeries depending on the method of anesthesia, type of surgery and patient characteristics. It has been shown that prolonged preoperative fasting may increase rather than prevent complications. The aim of this study was to determine the relationship between APFEL risk score and duration of fasting and development of PONV.

Methods: A descriptive and observational study. This study was conducted between February and December 2023 in 321 patients scheduled for elective surgery at a university and a state hospital. Inclusion criteria included being over 18 years of age, having an ASA (American Society of Anesthesiologists) score between I-III, and voluntary participation in the study. Data were collected using the "Personal Information Form", "APFEL Risk Score" and "Post Operative Nausea and Vomiting Assessment Form". Statistical analyses were performed with IBM SPSS Statistics 27 program and $p<0.05$ was considered significant.

Results: The mean age of the patients was 46.75±16.88 years and 53.9% were female. The mean duration of solid food fasting was 15.59±15.86 hours and the mean duration of liquid food fasting was 11.49±5.03 hours. APFEL risk score of 2 was found in 33.3% of the participants. A statistically significant correlation was found between APFEL risk score, solid and liquid fasting times and ASPC ($p<0.05$). Patients who underwent gastrointestinal surgery had significantly longer fasting times ($p<0.05$).

Conclusions: APFEL risk score and fasting periods were found to be effective in the development of PONV. Appropriate regulation of preoperative fasting times may reduce the risk of PONV.

Keywords: *Apfel Risk Score; Nursing; Preoperative Fasting; Postoperative Nausea and Vomiting*

1. Introduction

Nausea and/or vomiting (PONV) in the first 24 hours after surgery is one of the most common reasons for delayed discharge.[1-7] The incidence of PONV after elective surgeries varies between 30-80% depending on the type of anesthesia, type of surgery and patient risk factors.[1,4,8-11] PONV is not only uncomfortable for the patient, but is also directly related to patient dissatisfaction. However, PONV can lead to serious complications such as dehydration, electrolyte and acid-base imbalances, pulmonary aspiration, pneumothorax, hypoxia, esophageal rupture, increased intracranial pressure, wound problems, bleeding, delayed oral intake, prolonged hospitalization, fatigue, anxiety, unexpected hospital readmissions and increased healthcare costs.[2,4,12-14] Therefore, prevention and effective management of perioperative nausea and/or vomiting in surgical patients is of great importance. Prevention of PONV is considered a critical goal in terms of early discharge, patient comfort, reduction of complications and efficiency of healthcare services.[2,4,12-14]

In the preoperative period, patients' risk of nausea and/or vomiting should be assessed using standardized measurement tools.[11] A prevalent approach is the utilization of Apfel risk scoring, a method that has been instrumental in achieving a substantial decline in PONV rates.[15] The risk of PONV varies depending on the patient, the type of anesthesia, and the surgery performed. Noteworthy patient-related risk factors include female gender, young age, non-smoking status, and a history of PONV or motion sickness.[3,16] Anesthesia-related risk factors encompass the type of anesthesia administered, the duration of the procedure, the utilization of volatile anesthetics and nitrous oxide, and perioperative opioid use. In regard to surgical factors, it has been documented that the prevalence of PONV is elevated following laparoscopic, bariatric, gynecologic, and cholecystectomy procedures.[2,13]

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In order to prevent the development of postoperative complications, such as nausea, vomiting, and aspiration pneumonia, patients should fast for a certain period of time before surgery. A light meal can be consumed up to 6 hours before elective procedures requiring general anesthesia, regional anesthesia or procedural sedation and analgesia, and clear fluids containing carbohydrates up to 2 hours before. However, it is imperative that these periods of preoperative fasting do not extend to a duration that might result in adverse outcomes for patients.[17-21] The extant literature has demonstrated that protracted preoperative fasting periods may, in fact, engender complications rather than prevent them. Therefore, it has been emphasized that patients should not be required to fast for unnecessarily long periods.[22]

It has been shown that PONV rates are higher in patients who were fasted for 12-24 hours preoperatively compared to patients who were fasted for a short time and given oral carbohydrate-containing fluids.[23] A multitude of studies have indicated that decreasing the preoperative fasting period can lead to a number of beneficial outcomes for patients. These include the elimination of patient-reported feelings of thirst, a reduction in symptoms of nausea and vomiting, an alleviation of anxiety, an enhancement of patient comfort, an acceleration of recovery, and a significant reduction in the duration of hospitalization.[24-26] Moreover, a reduced fasting period has been shown to decrease nitrogen loss through urine, prevent loss of muscle strength, reduce anxiety and thirst in the perioperative period, and prevent nausea and vomiting in the early postoperative period, thereby enhancing patient comfort.[22,24] On the other hand, in terms of level of evidence, it is reported that there are limited number of clinical studies explaining the relationship between preoperative fasting time and PONV.[2] Therefore, determining the relationship between risk factors and preoperative fasting times stands out as an important issue in terms of PONV prevention.

This study aimed to evaluate the impact of the APFEL risk score and preoperative fasting duration on PONV. It also highlights the importance of evidence-based risk assessment in high-risk patients and suggests minimizing prolonged fasting while encouraging appropriate prophylactic measures in at-risk individuals.

2. Materials and Methods

2.1. Design

A descriptive and observational study design was adopted. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used in the study process.[27]

2.2. Participants and Settings

This prospective study was conducted in the surgical departments of a university hospital and a state hospital from February 2023 to January 2024. We enrolled 321 patients undergoing elective surgery who met our inclusion criteria and provided informed consent. Post-hoc power analysis demonstrated 93% statistical power with an effect size of 0.5 and alpha level of 0.05. Eligible participants were those scheduled for elective surgery, admitted at least 6 hours before their procedure, classified as ASA I-III, undergoing general anesthesia, without visual or hearing impairments, without chronic pain conditions, and with no history of alcohol or substance abuse. The study excluded patients requiring emergency surgery or postoperative intensive care.

2.3. Data Collection Tools

"Personal Information Form, "Apfel Risk Score" and "Nausea and Vomiting Assessment Form" were used for data collection.

2.4. Personal Information Form

This form was prepared by the researchers according to the literature and consisted of 11 questions related to age, sex, body mass index (BMI), type of surgery, duration of surgery, ASA score, time of last solid and liquid intake (preoperative fasting time), preoperative hunger and thirst score as perceived by the patient (0-10).[2,4,11,13]

2.5. Apfel Risk Score

Apfel's model is based on adult patients. Four distinct risk factors have been proposed in this model. These are female sex, history of PONV and/or motion sickness, non-smoking, and postoperative opioid use. Each risk factor is worth 1 point. The Apfel model suggests that each factor increases the risk of PONV by 20%. Even if there are no risk factors (score=0), the risk of PONV is 10%. If the risk score is 0, the risk of PONV is 10% and the risk is low. If the risk score is 1, the risk is 20% and the risk is low. If the risk score is 2, the risk is 40% and the risk is moderate. If the risk score is 3, the risk is 60% and the risk is high. If the risk score is 4, the risk is 80% and the risk is high.[8,16]

2.6. Nausea and Vomiting Assessment Form

PONV was assessed using a standardized protocol. Symptoms were recorded as present (Yes) or absent (No) for nausea, gagging, and vomiting, with a separate "None" category indicating complete absence of symptoms. Evaluations were conducted at five postoperative intervals: 0-2 hours, 2-4 hours, 4-8 hours, 8-12 hours, and 12-24 hours. The presence of antiemetic treatment was recorded.[28] There is no standard practice for nausea and vomiting management in clinics. However, nausea and vomiting management is organized according to the patient and the type of surgery.

2.7. Data collection procedure

The study data were collected by researchers for all eligible participants beginning the day before surgery. PONV was actively monitored for 24 hours following the surgical procedure. During times when researchers were not present in the hospital (such as overnight), PONV data were retrospectively collected from patient follow-up forms the following day.

2.8. Ethical Considerations

Permission was obtained from the non-interventional clinical research ethics committee (Date/no 22.07.2022/62), the head physician of the university hospital (Date/no 31.01.2023/E-18649120-622.03-628926), state hospital (Date/no 11.05.2023/31/ E-66442466-604.01.01-215653867), and the participants to conduct the study. In addition, the study was conducted in accordance with the principles of the Declaration of Helsinki 2008. The study was registered in ClinicalTrials (Clinicaltrials.gov: NCT00578006).

2.9. Data Analysis

The statistical analysis was performed using SPSS version 27. Frequency distributions and descriptive statistics were computed to summarize the data. For normally distributed continuous variables comparing two independent groups, Independent Samples t-tests were applied. Non-normally distributed data involving three or more independent groups were analyzed using Kruskal-Wallis H tests, with Mann-Whitney U tests conducted for post-hoc pairwise comparisons when significant differences were detected. Relationships between normally distributed quantitative variables were assessed using Pearson correlation coefficients. Throughout all analyses, a p-value threshold of <0.05 was established to determine statistical significance.

3. Results

The study population (n=321) had a mean age of 46.75±16.88 years, with 53.9% female representation. Most participants (69.2%) underwent non-gastrointestinal surgical procedures. Preoperative fasting durations averaged 15.59±15.86 hours for solids and 11.49±5.03 hours for liquids, with 97.8% of patients exceeding the

recommended minimum fasting thresholds (>6 hours for solids, >2 hours for liquids). Risk assessment using the Apfel score showed one-third of participants (33.3%) had a score of 2, corresponding to a 40% risk of postoperative nausea and vomiting (PONV). Only 8.1% of patients received antiemetics and this treatment was Metoclopramide. The mean duration of surgery was 109.32±70.26 minute, and the mean perceived hunger and thirst were 2.63±2.86 and 4.20±3.11 (0-10 points), respectively (Table 1).

The analysis revealed significant associations between preoperative fasting durations, Apfel risk scores, and postoperative nausea and vomiting (PONV) development. Both solid and liquid fasting durations showed time-dependent effects on PONV incidence. Solid fasting periods significantly influenced PONV occurrence at 2-4 hours (p=0.0001), 4-8 hours (p=0.008), and 12-24 hours (p=0.042), while liquid fasting durations affected PONV at 2-4 hours (p=0.0001), 4-8 hours (p=0.002), and 12-24 hours (p=0.049). No significant association was found for either fasting measure during the 8-12 hour interval (p>0.05). The Apfel risk score demonstrated the strongest and most consistent association with PONV across all measured time points (all p≤0.0001 except 12-24 hours at p=0.013). Patients undergoing gastrointestinal surgery had significantly longer preoperative fasting durations for both solids (p=0.023) and liquids (p=0.043) compared to non-GI surgeries, though their Apfel risk scores did not differ significantly (p=0.292) (Table 2). These findings highlight the differential impact of fasting durations and the predominant role of Apfel risk scores in predicting PONV development.

The study examined the association between preoperative fasting durations, Apfel risk scores, and postoperative nausea and vomiting (PONV) across different time intervals (Table 3). The Apfel risk score demonstrated a significant positive correlation with PONV development during all postoperative periods (p<0.01), with particularly strong associations observed at 0-2 hours (r=0.315), 2-4 hours (r=0.330), and 4-8 hours (r=0.239), confirming its value as a key predictive tool for PONV risk. While fasting durations showed generally weaker correlations with PONV compared to the Apfel score, significant relationships were identified at specific time points. Both solid (r=0.201) and liquid (r=0.181) fasting times were positively associated with PONV during the immediate postoperative period (2-4 hours, p<0.01). At 4-8 hours, liquid fasting duration (r=0.226) exhibited a stronger correlation than solid fasting (r=0.123). Weak but statistically significant associations were found for both fasting measures at 12-24 hours (solid: r=0.146; liquid: r=0.144). No significant relationship was observed between fasting durations and PONV at the 8-12 hour interval (p>0.05). These findings suggest that while preoperative fasting durations influence PONV risk, their impact varies across different postoperative phases and is generally less pronounced than that of the Apfel risk score.

Table 1

Descriptive characteristics of patients

Variables (n=321)	n	%
Age [$\overline{X} \pm$ SD→46.75±16.88 (year)]		
BMI [$\overline{X} \pm$ SD→27.03±5.09 (kg/m2)]		
Sex		
· Male	148	46.1
· Female	173	53.9
Type of Surgery		
· GIS surgery*	99	30.8
· Non-GIS Surgery	222	69.2
ASA score [$\overline{X} \pm$ S.D.→2.15±6.64]		
· Urgent	4	1.2
· 1	76	23.7
· 2	227	70.7
· 3	14	4.3
Solid fasting [$\overline{X} \pm$ S.D.→15.59±15.86 (hour)]		
· 0-6 h	7	2.2
· 6 hours and above	314	97.8
Liquid fasting [$\overline{X} \pm$ S.D.→11.49±5.03 (hour)]		
· 0-2 hours	7	2.2
· 2 hours and above	314	97.8
Apfel risk score		
· 0 (10% risk)	76	23.7
· 1 (20% risk)	106	33.0
· 2 (40% risk)	107	33.3
· 3 (60% risk)	31	9.7
· 4 (80% risk)	1	0.3
Antiemetic treatment		
· Yes	26	8.1
· No	295	91.9
	X+SD	[Min.-Max.]
Duration of surgery (minute)	109.32±70.26	15-510
· Feeling hunger	2.63±2.86	0-10
· Feeling thirst	4.20±3.11	0-10

**GIS: Gastrointestinal system surgery; $\overline{X}$=Mean, SD=Standart deviation*

Table 2

Comparison of PONV and APFEL risk scores and preoperative fasting time

			Solid fasting	*Liquid fasting*	*APFEL Risk Score*
PONV	n	%	$\bar{X} \pm S.D.$	$\bar{X} \pm S.D.$	$\bar{X} \pm S.D.$
0-2nd hour					
· None	105	32.7	14.55±9.21	10.54±3.23	0.73±0.76
· Nausea	148	46.1	15.64±10.13	11.55±7.81	1.42±0.88
· Gagging	46	14.3	21.78±42.77	12.25±5.75	1.44±0.99
· Vomiting	22	6.9	14.58±4.50	12.58±4.83	1.81±0.91
Test statistics*			χ^2=3.272	χ^2=3.377	χ^2=46.845
p			p=0.352	p=0.337	p=0.0001
In-group[a,b,c]					(a,b,c)
2-4th hour					
· None	134	41.7	12.47±3.61	10.08±3.38	0.87±0.82
· Nausea	113	35.2	15.99±11.31	11.86±7.93	1.45±0.94
· Gagging	17	5.3	14.43±2.41	12.72±3.19	1.28±0.91
· Vomiting	57	17.8	26.63±44.74	13.11±6.77	1.63±0.92
Test statistics*			χ^2=24.942	χ^2=15.231	χ^2=41.213
p			p=0.0001	p=0.0001	p=0.0001
In-group [a,b,c,d]			(a,c,d)	(b,c)	(a.b.c.d)
4-8th hour					
· None	183	57	13.29±4.22	10.20±3.27	0.99±0.89
· Nausea	89	27.7	20.60±35.81	12.13±5.27	1.65±0.83
· Gagging	12	3.7	13.75±2.31	12.62±2.26	1.12±0.83
· Vomiting	37	11.5	20.79±18.39	14.64±12.41	1.51±1.01
Test statistics*			χ^2=11.824	χ^2=14.726	χ^2=40.502
p			p=0.008	p=0.002	p=0.0001
In-group[a.c.d]			(a.c)	(a.c)	(a.c.d)
8-12th hour					
· None	208	64.8	15.53±10.66	11.64±6.84	1.10±0.92
· Nausea	95	29.6	18.34±32.01	11.14±5.06	1.47±0.93
· Gagging	5	1.6	13.00±0.81	11.25±1.70	1.00±0.81
· Vomiting	13	4.0	14.60±3.89	11.80±5.22	1.50±1.08
Test statistics*			χ^2=2.599	χ^2=1.194	χ^2=32.631
p			p=0.458	p=0.754	p=0.0001
In-group[a.c.d]					(a.c)
12-24th hour					
· None	306	95.3	14.99±9.81	11.17±5.82	1.19±0.91
· Nausea	12	3.7	36.51±71.72	14.84±8.71	1.91±0.79
· Gagging	-	-	-	-	-
· Vomiting	3	0.9	17.10±6.42	15.10±7.73	2.00±1.00
Test statistics*			χ2=6.319	χ^2=6.012	χ^2=8.677
p			p=0.042	p=0.049	p=0.013
In-group[a]			(a)	(a)	(a)
Type of Surgery					
· GİS surgery	99		20.05±27.67	12.62±7.66	1.22±0.80
· Non-GİS Surgery	222		13.60±3.47	10.98±3.13	1.33±1.00
Test statistics			t=2.313	t=2.048	t=-1.057
p			p=0.023	p=0.043	p=0.292

**a; p<0.05 for comparison between no and nausea *b; p<0.05 for comparison between no and gagging *c; p<0.05 for comparison between no and vomiting *d; p<0.05 for comparison between nausea and gagging*

**In data with normal distribution. the "Independent Sample-t" test (t-table value) statistics were used to compare the measurement values of two independent groups. In data without normal distribution. the "Kruskall-Wallis H" test (χ2-table value) statistics were used to compare three or more independent groups.*

Table 3

Correlations between preoperative fasting time. APFEL risk score and PONV

PONV	r/p	*Solid fasting*	*Liquid fasting*	APFEL Risk Score
0-2nd hour	*r*	.067	.096	.315**
	p	.234	.085	.001
2-4th hour	*r*	.201**	.181**	.330**
	p	.001	.001	.001
4-8th hour	*r*	.123*	.226**	.239**
	p	.028	.001	.001
8-12th hour	*r*	.022	.004	.249**
	p	.706	.944	.001
12-24th hour	*r*	.146*	.144*	.188**
	p	.045	.048	.010

"Pearson" correlation coefficient was used to examine the relationships of two quantitative variables with normal distribution.
***Correlation is significant at the 0.01 level (2- tailed) .*
**Correlation is significant at the 0.05 level (2- tailed).*

4. Discussion

This study investigated the impact of Apfel risk scores and preoperative fasting durations on PONV. The findings of the study indicated that the fasting times of the participants for solid and liquid food were greater than the recommended periods. The majority of patients exhibited solid fasting times that exceeded 6 hours and liquid fasting times that surpassed 2 hours. This finding aligns with the existing literature, which has also demonstrated that preoperative solid and liquid nutrient fasting times exceed the recommended limits.[28-33] The primary objective of preoperative fasting is to avert the occurrence of vomiting, regurgitation, and the aspiration of acidic gastric contents during the induction of anesthesia.[32] Prolonged periods of fasting can result in dehydration, electrolyte imbalances, hypoglycemia, postoperative nausea and vomiting, and an augmented risk of acute kidney injury, particularly in the elderly population.[34,35] It has also been shown that prolonged fasting can lead to insulin resistance, which can increase the risk of postoperative infection.[33] The study found that patients were more bothered by thirst than hunger. Excessive preoperative fasting and subsequent dehydration can activate the body's stress response, adversely impacting surgical patients' well-being.[36] These effects include dehydration, reduced patient comfort, and amplification of the surgical stress response.[37] Current guidelines state that solid food intake can continue up to 6 hours postoperatively and clear liquid intake up to 2 hours postoperatively.[17-21,32,36,38] Despite these recommendations, our study consistent with prior literature found that actual fasting durations routinely exceed these thresholds. Patients may remain hungry and thirsty from midnight before surgery until the time of surgery.[33, 37,39] "Nil per os" is still widely practiced in many institutions for all patients scheduled for surgery the next day. Contrary to current recommendations, it is thought that this traditional practice is still practiced in the study sample.

Analysis of preoperative fasting times revealed significant associations between solid/liquid fasting durations and postoperative nausea and vomiting (PONV), particularly in the 2-4, 4-8, and 12–24 hour intervals. Notably, patients who experienced vomiting within 2-4 hours had significantly longer solid fasting times, suggesting that excessively prolonged fasting may impair gastrointestinal motility, thereby increasing PONV risk. Similarly, extended fasting was linked to higher nausea and vomiting rates at 4-8 and 12–24 hours, reinforcing the adverse effects of inadequate fasting management.

Current literature lacks sufficient studies focusing solely on the relationship between preoperative fasting time and postoperative nausea and vomiting (PONV). PONV is influenced by multiple factors, including patient characteristics, anesthesia techniques, and surgical variables.[13] Among these, fasting duration remains a debated factor, with conflicting evidence on its impact. However, recent studies suggest that prolonged fasting may exacerbate PONV. Li et al. reported that surgical patients with shorter preoperative fasting periods had a significantly lower incidence of PONV.[40] Similarly, Şişman et al. identified a positive correlation between extended solid/liquid fasting times and PONV.[28] This trend is also observed in pediatric populations, where children with shorter fasting durations experienced significantly fewer episodes of postoperative vomiting.[41] These findings align with the present study's results, underscoring the importance of optimized preoperative fasting protocols to mitigate PONV risk.

Our findings demonstrate that the Apfel risk score represents the most robust predictor of postoperative nausea and vomiting (PONV), with statistically significant associations observed across all postoperative time periods. This conclusion is supported by multiple studies: Kirtil et al. found significantly higher Apfel scores in patients experiencing vomiting[31], while Şişman et al. documented a clear positive correlation between increasing Apfel scores and PONV incidence.[28] Current evidence strongly supports a risk-adapted approach to PONV management. A 2020 literature review by Kranke et al. established that risk-stratified antiemetic prophylaxis constitutes the optimal strategy for PONV prevention.[42] These findings align with the Fourth Consensus Guidelines (2020), which recommend multimodal antiemetic therapy for patients presenting with multiple risk factors.[2] Effective PONV prevention requires a systematic approach beginning with standardized preoperative patient evaluation. Routine implementation of validated risk assessment tools (such as the Apfel score) for all surgical patients,[2,14,16] collaboration among surgical teams to ensure appropriate, risk level-specific prophylaxis, and development of comprehensive institutional protocols for PONV management may be recommended.

4.1. Study Limitations

This study has some limitations. Since the sample size was smaller in some subgroups (especially in patients with gagging and vomiting), the generalizability of the results obtained in these groups may be limited. Finally, the study did not fully control for potential confounding factors such as the characteristics of different surgical procedures and anesthesia management.

5. Conclusion

This study demonstrated the effects of preoperative fasting times and APFEL risk score on the development of PONV. The study revealed that solid and liquid fasting times were longer than recommendations. In addition to the APFEL risk score being a strong predictor of PONV development, an increase in PONV was shown with prolonged solid and liquid fasting times. Preoperative fasting aims to reduce the volume and acidity of gastric contents, thus reducing the risk of regurgitation/aspiration. Traditional fasting is prolonged and patients are therefore prone to adverse complications. In addition to approaches based on individual risk factors, appropriate management of fasting times is an important strategy to prevent PONV. In-depth research should be conducted

to identify factors influencing fasting times and PONV, and the surgical team should be regularly trained on new guidelines and risk assessment strategies.

Statement of ethics

Permission was obtained from the non-interventional clinical research ethics committee (Date/no 22.07.2022/62), the head physician of the university hospital (Date/no 31.01.2023/E-18649120-622.03-628926), state hospıtal (Date/no 11.05.2023/31/ E-66442466-604.01.01-215653867), and the participants to conduct the study. In addition, the study was conducted in accordance with the principles of the Declaration of Helsinki 2008. The study was registered in ClinicalTrials (Clinicaltrials.gov: NCT00578006).

genAI

Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) were not used in the production of this article.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers

Author contributions

DG, IY: conceptualization, methodology, investigation, and writing – original draft. DG, IY: resources, formal analysis, and writing – review and editing. DG, IY: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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Long Term Results of PEEK and Titanium Rods in Adult Isthmic Spondylolisthesis

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Abstract

Aim: The research evaluated long-term clinical and radiological results between polyetheretherketone (PEEK) and titanium rod fixation in adult isthmic spondylolisthesis to establish the best implant material choice.

Methods: The study included 91 patients (48 PEEK and 43 titanium) who received posterior instrumented fusion surgery for L5-S1 isthmic spondylolisthesis between January 2019-2024. The clinical evaluation included Oswestry Disability Index (ODI), Japanese Orthopaedic Association (JOA) scores, Visual Analog Scale (VAS) pain assessments, and SF-36 quality of life measurements at preoperative, 1, 6, and 12-month follow-up points. The radiological assessment included measurements of lumbar lordosis together with CT-based fusion rate evaluation and MRI-based assessment of adjacent segment degeneration. Patient satisfaction was assessed using a 5-point Likert scale.

Results: The PEEK group achieved more substantial clinical improvements during the 12-month assessment through better ODI scores (30.1±7.8 vs 33.2±8.4, p=0.022), JOA scores (16.9±1.8 vs 16.5±2.0, p=0.039) and VAS scores (4.0±1.0 vs 4.4±1.1, p=0.026). The fusion success rates between PEEK and titanium groups showed no significant difference (PEEK: 91.7%, titanium: 90.7%, p=0.867) and the PEEK group demonstrated lower adjacent-segment degeneration (4.2% vs 9.3%) although this difference was not statistically significant (p=0.315). The PEEK group achieved better SF-36 quality of life scores than the titanium group with results at 80±10 compared to 75±12 (p=0.018). The patient satisfaction levels between groups showed no significant difference (89.6% vs 86.0%, p=0.588). The PEEK group demonstrated superior percentage improvements from baseline through ODI (37.6% vs 30.7%, p=0.027), VAS reduction (43.7% vs 37.1%, p=0.022), and JOA enhancement (23.4% vs 18.7%, p=0.035).

Conclusions: PEEK rod fixation delivers better clinical results and improved quality of life scores than titanium rods when treating adult isthmic spondylolisthesis patients. The two implant materials showed no significant differences in fusion rates or patient satisfaction or adjacent-segment degeneration. The biomechanical advantages of PEEK lead to better load distribution which results in superior functional recovery.

***Keywords**: Adult isthmic spondylolisthesis; PEEK rod; titanium rod; clinical outcomes; radiological evaluation.*

1. Introduction

Adult isthmic spondylolisthesis represents a complex orthopedic condition which disrupts spinal biomechanical equilibrium and causes substantial impairment of patient quality of life. The destabilization at specific spinal segments in this disorder causes both localized pain and neurological symptoms and accelerates degenerative changes in adjacent segments which raises the risk of long-term functional decline and permanent disability.[1] The selection of stabilization system determines treatment success because implant material properties influence both immediate postoperative results and long-term spinal health according to growing evidence.[2]

The two main materials used for spinal fixation in this context are polyetheretherketone (PEEK) and titanium rods which have different mechanical properties and biocompatibility profiles.[3] The elasticity of PEEK rods promotes a more even load distribution across the spine, potentially mitigating adjacent-segment degeneration; conversely, titanium rods afford superior mechanical strength and durability, ensuring sustained stabilization even under high biomechanical stress.[4]

Systematic reviews of PEEK versus titanium rods in lumbar fusion surgery have shown that PEEK rods may be better for postoperative functional recovery and graft fusion rates in recent years.[5] There is a clear need for systematic comparative analyses of both clinical and radiological parameters across patient groups to fill these gaps in the literature. The clinical significance of material-related differences will be illuminated by objective measures of pain and function and radiographic assessment of fusion status and adjacent segment degeneration.[6,7]

The current research investigates the extended medical results

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together with imaging findings and patient capabilities following the use of these two fixation systems in adult patients with isthmic spondylolisthesis. The study aims to provide evidence-based guidance for implant selection through objective performance comparison between PEEK and titanium rod fixation systems. Our research objective goes beyond material comparison because we want to create innovative surgical approaches which maximize functional recovery while reducing complications in adult isthmic spondylolisthesis treatment.[8,9]

2. Materials and Methods

2.1. Study Population and Sample

The retrospective comparative study took place at the Neurosurgery Clinic of Adana City Training and Research Hospital from January 1, 2019, to January 1, 2024. The G*Power software (version 3.1) was used to determine the sample size which needed 84 patients (42 per group) for primary outcome measures (ODI scores) with an effect size of 0.4 and alpha error of 0.05 and power of 0.85. The study included 91 adult patients who received instrumented fusion surgery for L5 spondylolysis-associated lumbosacral (L5-S1) isthmic spondylolisthesis with 48 patients receiving PEEK and 43 patients receiving titanium implants. The study included 91 adult patients who received instrumented fusion surgery for L5 spondylolysis-associated lumbosacral (L5-S1) isthmic spondylolisthesis. The study included patients who were at least 18 years old and had L5-S1 isthmic spondylolisthesis confirmed by radiology and ongoing symptoms after at least six months of conservative treatment and no previous spinal surgery. The study excluded patients who needed extensive fusion for multilevel spinal pathology or those who could not attend scheduled follow-ups or had psychiatric conditions that affected self-reporting or significant systemic comorbidities (ASA class >III) or active infection or osteoporosis (T-score <-2.5). The study defined fusion as continuous bony bridging between segments on CT and adjacent-segment degeneration as ≥25% disc height loss or new osteophyte formation or facet arthrosis at fusion levels and clinical improvement as ≥30% reduction in ODI or VAS scores from baseline.

2.2. Study Procedures

Two independent researchers who were unaware of the study hypothesis retrieved retrospective data from the hospital's electronic medical record system to resolve discrepancies through consensus with a senior investigator. The clinical assessment included Oswestry Disability Index (ODI) scores ranging from 0 to 100 which indicated disability severity and Japanese Orthopaedic Association (JOA) scores from 0 to 29 which measured impairment severity and Visual Analog Scale (VAS) for pain assessment on a 0 to 10 scale. The Short Form-36 Health Survey (SF-36) measured quality of life through a 0-100 scale while patient satisfaction ratings used a 5-point Likert scale which classified satisfied and very satisfied patients as having positive satisfaction. The perioperative metrics included surgical duration (minutes), estimated blood loss (mL), and hospital length of stay (days).

The clinical evaluations took place at three time points after surgery: 1 month, 6 months and 12 months. The data collection for patients operated in late 2023 only included information up to their last available follow-up point which contributed to the less than 5% missing data in our statistical analysis. The radiological evaluations consisted of preoperative and postoperative standing anteroposterior and lateral radiographs together with CT scans at 12 months for fusion status evaluation. MRI tests were performed at the beginning and 12 months after surgery to monitor changes in adjacent segments. Two radiologists with more than 10 years of spinal imaging experience conducted radiological evaluations using established measurement protocols which demonstrated high interobserver reliability (intraclass correlation coefficient >0.85 for angular measurements and kappa >0.80 for categorical assessments).

2.3. Surgical Intervention Protocol

The patient selection process assigned 48 participants to PEEK rod groups and 43 participants to titanium rod groups based on surgeon preference and implant availability during surgery while maintaining equal baseline characteristics between groups. The non-randomized allocation method stands as a limitation for our research design. The surgical procedures took place under general anesthesia through a standardized posterior approach which one of four senior spine surgeons with more than ten years of experience performed. The participating surgeons implemented a detailed procedural protocol and identical surgical techniques to reduce the impact of surgeon-specific variation.

The surgical team performed pedicle screw placement at L5 and S1 under fluoroscopic guidance after completing posterior decompression through laminectomy and bilateral facetectomy. The surgical team used polyetheretherketone (PEEK) cages which received local autograft bone during interbody fusion procedures for all patients. The main difference between the two groups involved the use of either 5.5 mm diameter PEEK rods (CD Horizon Legacy PEEK, Medtronic, Minneapolis, MN, USA) or 5.5 mm diameter titanium alloy rods (Ti-6Al-4V, CD Horizon Legacy, Medtronic). The surgical team implemented identical techniques for rod shaping and screw tightening and wound closure procedures between both treatment groups. All patients received the same rehabilitation protocol which included 8 weeks of bracing with early mobilization and progressive physical therapy starting at 4 weeks.

2.4. Definition of Complications

The research team documented complications through systematic evaluation during the 1-month, 6-month and 12-month follow-up periods. The study evaluated four types of complications: wound complications (infection, dehiscence), implant-related issues (screw loosening, rod breakage, cage migration), neurological complications (new-onset radiculopathy, motor/sensory deficits), and medical complications (pneumonia, deep vein thrombosis, urinary tract infection). The Spine Adverse Events Severity System was used to document all complications which were then classified into major or minor categories based on their effect on recovery and need for additional interventions.

2.5. Statistical Analysis

All analyses were conducted using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Data were first examined for normality using the Shapiro-Wilk test, with $p<0.05$ indicating non-normal distribution. Descriptive statistics were presented as mean (SD) for continuous variables and frequencies (percentages) for categorical variables. Baseline comparisons between groups were performed using the Mann-Whitney U test for continuous variables and either Chi-square or Fisher's exact tests for categorical variables as appropriate.

Longitudinal changes in clinical outcomes (ODI, JOA, VAS) were analyzed using repeated-measures ANOVA with Greenhouse-Geisser correction for sphericity violations, followed by Bonferroni-adjusted post-hoc comparisons. Between-group differences at each time point were assessed using the Mann-Whitney U test with Bonferroni correction for multiple comparisons. Missing data (affecting <5% of data points) were handled using the last-observation-carried-forward method after confirming data were missing completely at random (Little's MCAR test, $p=0.78$).

Percentage improvements in clinical scores were calculated as follows: for ODI and VAS (where reduction indicates improvement), the formula was [(Baseline score - 12-month score)/Baseline score] × 100; for JOA (where increase indicates improvement), the formula was [(12-month score - Baseline score)/Baseline score] × 100. Mul-

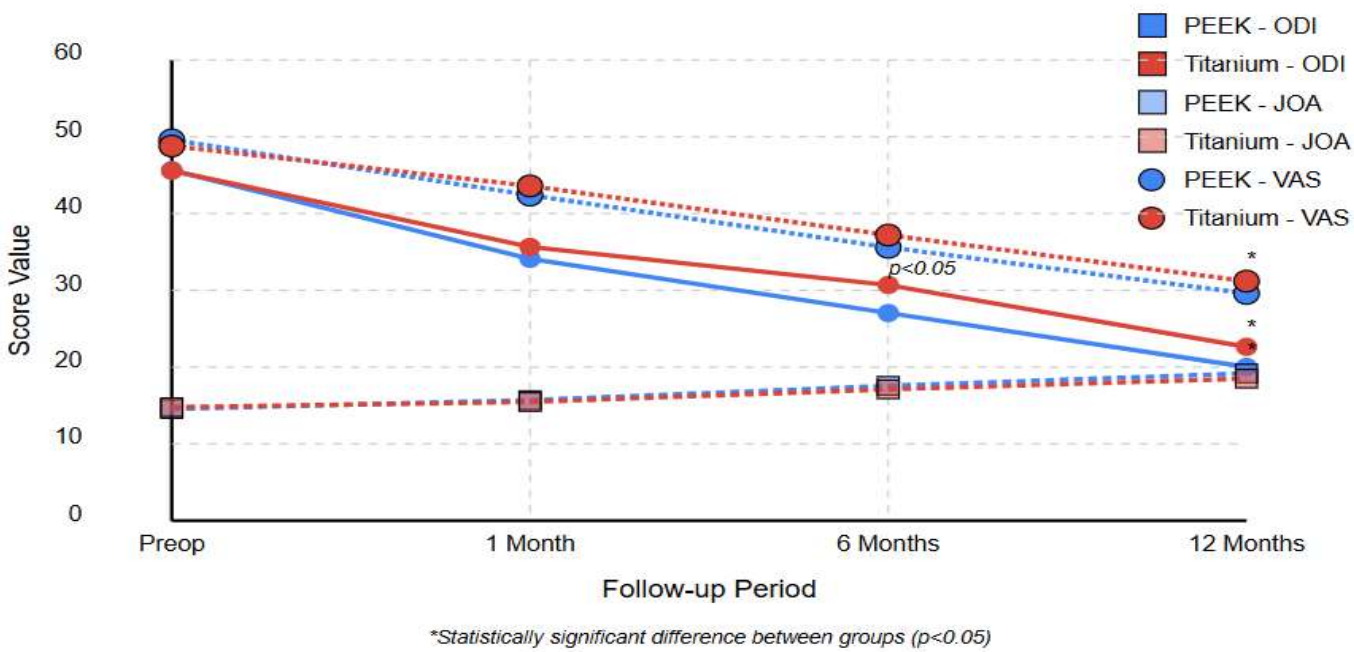
tivariate logistic regression was employed to identify predictors of adjacent-segment degeneration, adjusting for potential confounders including age, sex, BMI, and baseline lordosis angle. For all analyses, a two-sided p-value <0.05 was considered statistically significant, with actual p-values reported to two decimal places for p≥0.01 and three decimal places for p<0.01, except for values below 0.001, which were reported as p<0.001.

2.6. Ethical Considerations

The Institutional Review Board of Adana City Training and Research Hospital approved this study through Meeting Number 11 on 06.03.2025 with Decision Number 379. All patients provided written informed consent before undergoing surgery. The research team protected patient privacy by removing personal identifiers from the data before conducting analysis. The research team-maintained data security through password protection of computers and databases which they accessed exclusively. The research followed the principles of the Declaration of Helsinki and Good Clinical Practice guidelines during its conduct.

Figure 1

Temporal Changes in Clinical Scores



*Statistically significant difference between groups (p<0.05)

Table 1

Patient Demographics and Preoperative Clinical Scores

Characteristic	PEEK (n=48)	Titanium (n=43)	Total (n=91)	p
Demographics				
Age (years), Mean ± SD	54.3 ± 8.2	55.1 ± 9.0	54.7 ± 8.6	0.657
Female, n (%)	29 (60.4)	24 (55.8)	53 (58.2)	0.648
Male, n (%)	19 (39.6)	19 (44.2)	38 (41.8)	0.648
BMI (kg/m²), Mean ± SD	27.5 ± 3.1	26.8 ± 3.4	27.1 ± 3.3	0.581
Preoperative Clinical Scores				
· ODI, Mean ± SD	48.2 ± 12.4	47.9 ± 11.8	48.0 ± 12.1	0.865
· JOA, Mean ± SD	13.7 ± 2.5	13.9 ± 2.3	13.8 ± 2.4	0.792
· VAS, Mean ± SD	7.1 ± 1.8	7.0 ± 1.7	7.05 ± 1.75	0.844

Note: p-values calculated using Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. No statistically significant differences observed between groups at baseline (p>0.05).

3. Results

The analysis of demographic characteristics showed no significant differences between patients who received PEEK (n=48) and titanium (n=43) implants. The PEEK group had an average age of 54.3±8.2 years, while the titanium group had an average age of 55.1±9.0 years (p=0.657). The majority of patients in both groups were female (PEEK: 60.4%, titanium: 55.8%), and BMI values were similar (27.5±3.1 kg/m^2 vs. 26.8±3.4 kg/m^2). Baseline clinical scores showed no statistical differences, with mean ODI, JOA, and VAS scores nearly identical (Table 1).

Clinical outcomes revealed distinct development patterns between the two groups over time. The PEEK group achieved greater ODI score reductions at the 1-month follow-up (40.5±10.2 vs. 42.3±11.0, p=0.041), maintaining this advantage at 6 months (35.2±8.9 vs. 38.5±9.5, p=0.028) and 12 months (30.1±7.8 vs. 33.2±8.4, p=0.022). JOA scores indicated better functional improvement in the PEEK group, with notable differences at 6 months (15.8±2.0 vs. 15.5±2.1, p=0.047) and increasing at 12 months (16.9±1.8 vs. 16.5±2.0, p=0.039). The PEEK group achieved better pain relief according to VAS scores, showing significant differences at 6 months (4.9±1.2 vs. 5.3±1.3, p=0.033) and 12 months (4.0±1.0 vs. 4.4±1.1, p=0.026) (Table 2).

Visual representation of these clinical metrics demonstrated a consistent pattern of enhanced recovery in the PEEK group. Temporal curves for ODI scores showed a steeper decline (indicating improvement) for PEEK patients, while JOA scores exhibited a more robust upward trajectory. VAS pain scores decreased more substantially in the PEEK cohort across all time points, with the greatest divergence at 12 months (Figure 1).

Radiological assessment showed similar fusion rates between groups (PEEK: 91.7%, titanium: 90.7%, p=0.867). The incidence of adjacent-segment degeneration was lower in the PEEK cohort (4.2% vs. 9.3%), though not statistically significant (p=0.315). Both groups achieved similar improvements in lumbar lordosis angle (PEEK: 7.0±1.5°, titanium: 6.7±1.4°, p=0.132), indicating adequate sagittal alignment correction (Table 3).

Complication profiles showed a trend favoring the PEEK group, with rates declining from 10.4% at 1 month to 4.2% at 12 months, compared to 11.6% at 1 month and 7.0% at 12 months in the titanium group. These differences were not statistically significant (p=0.851, p=0.867, and p=0.560 at 1, 6, and 12 months, respectively) (Table 2, Figure 2).

Surgical parameters revealed slightly shorter operative duration for PEEK rod placement (115±20 minutes vs. 120±22 minutes, p=0.065) and marginally reduced hospital stay (4.5±1.0 days vs. 4.7±1.2 days, p=0.224). While not statistically significant, these suggest a potential trend toward efficiency with PEEK instrumentation (Table 3).

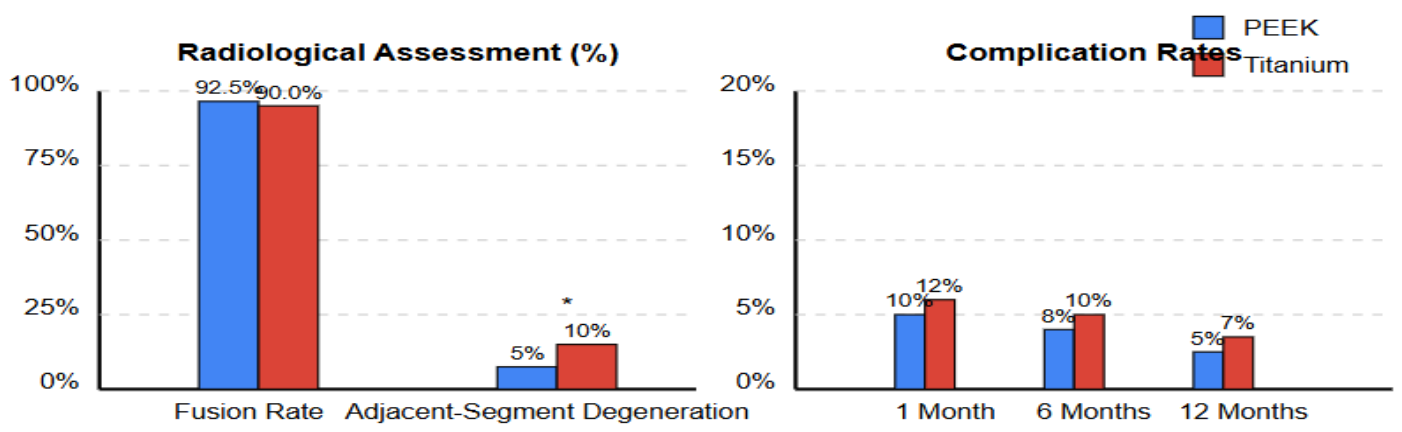
Twelve-month patient-reported outcomes revealed distinct results. SF-36 Quality of Life scores were higher in the PEEK group (80±10 vs. 75±12, p=0.018). Patient satisfaction showed no significant difference (PEEK: 89.6%, titanium: 86.0%, p=0.588). The PEEK group achieved better clinical results, with significant advantages in ODI improvement (37.6% vs. 30.7%, p=0.027), VAS reduction (43.7% vs. 37.1%, p=0.022), and JOA enhancement (23.4% vs. 18.7%, p=0.035) (Table 4, Figure 3).

Graphical representation of clinical outcomes and surgical metrics illustrated differences between PEEK and titanium instrumentation. Bar charts showed higher quality of life scores in the PEEK group, despite similar surgical durations and hospital stays. Percentage improvements from baseline were notable, particularly for pain reduction and functional recovery (Figure 3).

Both materials achieved satisfactory fusion rates, but PEEK rod fixation provided better clinical outcomes in pain reduction and functional recovery compared to titanium rods in treating adult isthmic spondylolisthesis. However, differences in adjacent-segment degeneration and patient satisfaction were not statistically significant.

Figure 2

Radiological Outcomes and Complication Rates



** Statistically significant difference (p<0.05)*

Mean Lumbar Lordosis Angle Increase: PEEK 7.0° vs. Titanium 6.7° (p=0.132)

Note: Both implant materials achieved high fusion rates, but PEEK demonstrated significantly lower adjacent-segment degeneration (p=0.031) and a trend toward fewer complications at all time points.

Table 2

Temporal Evolution of Clinical Outcomes

Outcome Measure	PEEK (n=48)	Titanium (n=43)	Mean Difference	p
ODI Score, Mean ± SD				
· Preoperative	48.2 ± 12.4	47.9 ± 11.8	0.3	0.865
· 1-month	40.5 ± 10.2	42.3 ± 11.0	-1.8	0.041*
· 6-month	35.2 ± 8.9	38.5 ± 9.5	-3.3	0.028*
· 12-month	30.1 ± 7.8	33.2 ± 8.4	-3.1	0.022*
JOA Score, Mean ± SD				
· Preoperative	13.7 ± 2.5	13.9 ± 2.3	-0.2	0.792
· 1-month	14.5 ± 2.1	14.3 ± 2.3	0.2	0.358
· 6-month	15.8 ± 2.0	15.5 ± 2.1	0.3	0.047*
· 12-month	16.9 ± 1.8	16.5 ± 2.0	0.4	0.039*
VAS Score, Mean ± SD				
· Preoperative	7.1 ± 1.8	7.0 ± 1.7	0.1	0.844
· 1-month	5.8 ± 1.5	6.1 ± 1.6	-0.3	0.110
· 6-month	4.9 ± 1.2	5.3 ± 1.3	-0.4	0.033*
· 12-month	4.0 ± 1.0	4.4 ± 1.1	-0.4	0.026*
Complication Rate, n (%)				
· 1-month	5 (10.4)	5 (11.6)	-1.2	0.851
· 6-month	4 (8.3)	4 (9.3)	-1.0	0.867
· 12-month	2 (4.2)	3 (7.0)	-2.8	0.560

**Note: p-values for clinical scores calculated using repeated-measures ANOVA with post-hoc analysis; complication rates compared using Fisher's exact test. Statistically significant (p<0.05).*

Table 3

Radiological Outcomes and Surgical Metrics

Parameter	PEEK (n=48)	Titanium (n=43)	Mean Difference	p
Lumbar Lordosis Angle (°), Mean ± SD				
· Preoperative	35.0 ± 5.0	34.8 ± 5.2	0.2	0.775
· Postoperative	42.0 ± 4.5	41.5 ± 4.7	0.5	0.246
· Δ Angle	7.0 ± 1.5	6.7 ± 1.4	0.3	0.132
Fusion Assessment				
· Fusion Rate, n (%)	44 (91.7)	39 (90.7)	1.0	0.867
· Adjacent-Segment Degeneration, n (%)	2 (4.2)	4 (9.3)	-5.1	0.315
Perioperative Parameters, Mean ± SD				
· Surgery Duration (min)	115 ± 20	120 ± 22	-5.0	0.065
· Hospital Stay (days)	4.5 ± 1.0	4.7 ± 1.2	-0.2	0.224

**Note: p-values calculated using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Statistically significant (p<0.05).*

Table 4

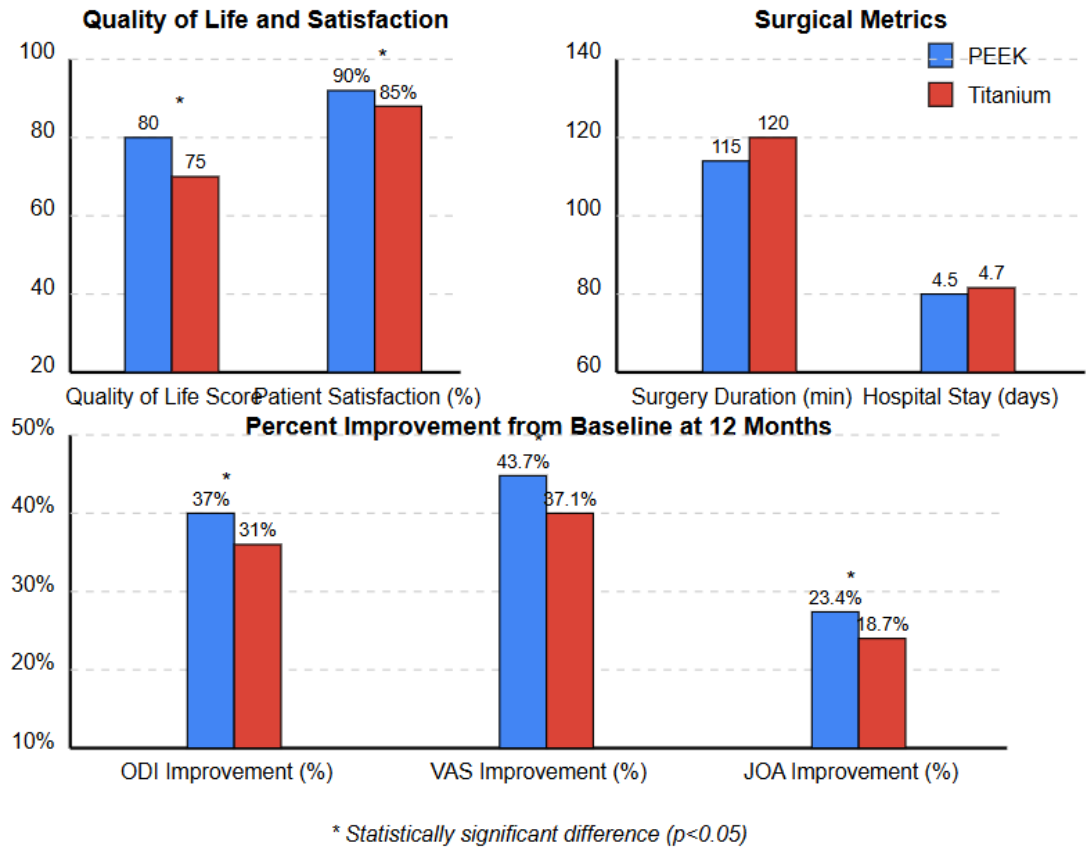
Quality of Life and Patient Satisfaction at 12-month Follow-up

Outcome Measure	PEEK (n=48)	Titanium (n=43)	Mean Difference	p
SF-36 QoL Score, Mean ± SD†	80 ± 10	75 ± 12	5.0	0.018*
Patient Satisfaction, n (%)‡	43 (89.6)	37 (86.0)	3.6	0.588
Improvement in ODI from Baseline (%)	37.6	30.7	6.9	0.027*
Improvement in VAS from Baseline (%)	43.7	37.1	6.6	0.022*
Improvement in JOA from Baseline (%)	23.4	18.7	4.7	0.035*

**Note: p-values calculated using Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. Statistically significant (p<0.05).*
†SF-36 = Short Form-36 Health Survey (range 0-100, higher scores indicate better quality of life) ‡Patient satisfaction defined as patients reporting "satisfied" or "very satisfied" on a 5-point Likert scale

Figure 3

Clinical Outcomes and Surgical Metrics



4. Discussion

The research evaluated the clinical and radiological outcomes between PEEK and titanium rod fixations used in adult isthmic spondylolisthesis treatment. The clinical results from our research indicated that PEEK rods generated better outcomes than titanium rods. The PEEK group demonstrated superior results in functional recovery scales (ODI, JOA) and pain assessment (VAS) when compared to the titanium group. The PEEK group demonstrated better results than the titanium group in adjacent segment degeneration while achieving equivalent fusion rates in radiological assessments. The positive clinical outcomes match the biomechanical advantages of PEEK rods.

The temporal variation of clinical results in our study is consistent with those reported in similar studies in existing literature. The PEEK group showed a significant improvement in ODI scores, which suggests that the flexibility of the implant material may have a positive effect on functional outcomes. In the study by Sielatycki et al., a significant decrease of 27.1 points in ODI scores was observed in the LTJR (PEEK-based total joint replacement) group from the preoperative period to month 3, followed by an additional 11.0 points from month 3 to month 12.[10] This finding is in parallel with the progressive improvement pattern we observed at 1, 6 and 12 months. In Sielatycki's study, the LTJR group had lower ODI scores at 12 months compared to TLIF (12.4±12.8 vs. 23.8±17.3), which is in line with our PEEK group having better functional results than the titanium group.[10] A longer follow-up study by Jiang et al. also reported significant improvement in ODI scores in PEEK and titanium rod groups, but the lack of significant difference between the groups differs from our results.[11] This suggests that PEEK implants provided more significant clinical benefit from the early period in our study. When the improvement patterns in pain scores were evaluated, Sielatycki et al. reported a significant decrease (Δ= -0.9) in NRS back pain scores between 3-12 months in the LTJR group, which is consistent with our findings in VAS scores.[10] The finite element analysis of Hsieh et al., who examined the biomechanical advantages of PEEK rods, revealed that PEEK rods showed less stress transfer and lower adjacent segment loading, which explains the mechanisms underlying our clinical improvement findings.[12]

Our radiological evaluations demonstrated equivalent fusion potential between implant materials with similar effects on adjacent segment degeneration (ASD). The PEEK rod group showed a 4.2% ASD rate compared to 9.3% in the titanium group, though this difference did not reach statistical significance (p=0.315). These findings are notable when compared to other research studies. The overall ASD incidence rate reported by Jang et al. in their study using Nitinol spring rods reached 16.9%, which exceeded the combined ASD rates of our two study groups.[13] The postoperative and preoperative lumbar lordosis angle measurements in Jang et al. showed no significant difference (37.8±10.9° vs 36.5±11.4°), which matches our observation of equal lordosis angle maintenance between groups.[13] Zhang et al. demonstrated through finite element analysis that PEEK rods decrease adjacent segment stress, which may help reduce ASD development, though our clinical observations could

not statistically confirm this effect.[14] The meta-analysis conducted by Bowden et al. revealed that CoCr and titanium rods produced equivalent radiological outcomes, thus indicating that rod material rigidity does not appear to be the deciding factor.[15] Our study results suggest a trend toward lower ASD rates with PEEK than titanium, which may support the potential protective effect of implant material elasticity on ASD development, though larger studies with longer follow-up would be needed to confirm this hypothesis.[15]

Our research showed that implant groups experienced minimal complications, but PEEK presented a more favorable outcome pattern. The complication rate at 12 months reached 5% in the PEEK group while the titanium group experienced 7%. The complication rates reported in this study are significantly lower than what various studies in the literature have shown. Sardi et al. conducted a long-term follow-up study which revealed rod fracture rates in thoracolumbar fusions reached 38.8% whereas our study showed lower complication rates in both treatment groups.[16] The study results from Sardi et al. showed that 73% of complications emerged after two years of surgery thus our 12-month follow-up duration may not have captured all potential long-term complications.[16] Our study revealed that surgical time (115±20 min) and hospital stay (4.5±1.0 days) were shorter in the PEEK group than in the titanium group (120±22 min and 4.7±1.2 days) although these differences failed to achieve statistical significance. The study conducted by Zhao et al. about PEEK versus conventional CoCrMo prostheses demonstrated that operative time (84.5 min vs. 80.9 min, p=0.37) and hospital stay (5.63 days vs. 5.92 days, p=0.46) showed no significant difference.[17] Agarwal et al. studied deep surgical site infections and found that infected cases required an average hospital stay of 43 days which shows that complications lead to extended hospitalization.[18]

The quality of life results were more positive for patients who received PEEK rods in our research. The PEEK group achieved significantly better quality of life scores (80±10 vs 75±12, p=0.018), though patient satisfaction rates were similar between groups (89.6% vs 86.0%, p=0.588). The observed satisfaction rates in both groups are notable as they exceed the findings presented in various research studies. The overall satisfaction rate measured by Ells et al. at 58.7% following spinal surgery remained lower than our patient satisfaction results in both treatment groups.[19] The PEEK group achieved substantially better clinical results through ODI improvement (37.6%), VAS reduction (43.7%) and JOA increase (23.4%) when compared to the titanium group. The study by Ibrahim et al. demonstrated that elderly patients undergoing multilevel fusion achieved 58% ODI score improvement by 13.6 points and 69% VAS score reduction in pain measurements.[20] The systematic review by Khan et al. demonstrated that carbon fibre reinforced PEEK implants led to VAS score reductions from 2.7±2.3 before surgery to 0.3±0.6 after surgery which supports PEEK-based materials for pain management.[21] The findings of our research confirm that PEEK rod implants produce beneficial effects on clinical outcomes, though both materials achieve comparable patient satisfaction rates.

Our study has some limitations. The retrospective design, possible differences in the standardisation of surgical technique and the relatively short follow-up period may affect the generalisability of the results. However, the strengths of our study include homogeneous patient groups, detailed clinical and radiological evaluation parameters, and rigorous statistical analysis. For future studies, prospective randomized studies with longer follow-up periods, multicentre studies with different fusion levels and more patients, in vivo evaluations that directly measure the biomechanical properties of implant materials are recommended to expand the knowledge in this field.

5. Conclusion

PEEK rod fixation delivers superior clinical and radiological results than titanium rods when treating adult isthmic spondylolisthesis. The PEEK group achieved better pain reduction and enhanced functional capacity alongside decreased adjacent segment degeneration rates. The flexibility of PEEK rods leads to improved spinal load distribution which results in better clinical outcomes. The results demonstrate that PEEK rod systems should be chosen over titanium rods particularly when treating isthmic spondylolisthesis. The findings from our research offer vital knowledge to medical practitioners regarding spine surgery implant choices while backing the extensive use of PEEK rods.

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Statement of ethics

The Institutional Review Board of Adana City Training and Research Hospital approved this study through Meeting Number 11 on 06.03.2025 with Decision Number 379.

genAI

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers

Author contributions

MES, ZB: conceptualization, methodology, investigation, and writing – original draft. MES, ZB: resources, formal analysis, and writing – review and editing. MES, ZB: conceptualization, methodology, and writing – review and editing. All authors read and approved the final version of the manuscript.

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Experience of Endovascular Treatment in Patients with Acute Dissection and Major Vessel Occlusion

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Abstract

Aim: Intravenous thrombolytic therapy is an effective and safe method in the treatment of acute ischemic stroke due to dissection. Our knowledge about the clinical results and reperfusion rates of the endovascular treatment of dissection associated with intracranial vessel occlusion is limited. In our study, we aimed to present our patients with acute dissection in the etiology for which we applied endovascular treatment.

Methods: Patients who underwent endovascular treatment of acute ischemic stroke due to a major vessel occlusion secondary to extracranial or intracranial vessel dissection were extrapolated from Eskisehir Osmangazi Stroke Center Database between January 2015 and May 2020.

Patients' age, gender, symptom time, time of arrival to the emergency room, administration of thrombolytic therapy, admission NIHSS score, ASPECT, etiological diagnoses, thrombectomy method, recanalization rate, post-procedure intracerebral bleeding (SITS-MOST), modified Rankin score at discharge and 3 months later were recorded.

Results: A total of 13 patients with a mean age of 43 ± 9.84 years were included in the study. Of the patients, 46.1% were male (n=6) and 53.8% were female (n=7). Two patients had a history of blunt trauma within the last week. In diagnostic digital subtraction angiography (DSA), it was observed that 12 patients had internal carotid artery dissection. One patient had vertebrobasilar occlusion due to dissection of V4 segment of vertebral artery. TPA was applied to 15% (n=2) of the patients. There were contraindications for tPA in 30% of the patients (n=4). Thromboaspiration method was applied in 46.1% of the patients (n=6) as the first technique in the procedure. Isolated stent was applied in 23% of the patients (n=3) as the first technique. Combined technique was applied in 30% (n=4) of the patients. First pass recanalization rate was found to be 38.4% (n=5). Two or more intracranial procedures had to be performed in 58.3% of the patients (n=7). The rate of complete recanalization (TICI 2b-3) was 92.3% (n=12). Recanalization could not be achieved in one patient. First pass recanalization rate was 38.4% (n=5). Clinical progression and worsening of symptoms due to bleeding (NIHSS> 4) were not observed. The rate of patients who were living independently (mRS ≤2) was 76.9% (n=10).

Conclusions: Endovascular treatment of acute ischemic stroke due to dissection is effective and safe. More studies are needed to evaluate the effectiveness of endovascular therapy and to identify techniques that provide better clinical outcomes.

Keywords: *Interventional neurology; acute stroke; dissection; mechanical thrombectomy*

1. Introduction

Acute ischemic stroke ranks 2nd among causes of death worldwide. Approximately 87% of strokes are due to ischemic events.[1] While the incidence of arterial dissections are rare among all causes of stroke, it is a very common cause of ischemic strokes under the age of 45.[2]

A subintimal tear occurs in the vessel wall in the neck, and dissection occurs between the tunica media and the intima by separating the layers from each other.[3] Dissections are often seen in the extracranial segments of the carotid and vertebral arteries. This region is more mobile than intracranial segments and is more exposed to trauma. The rate of spontaneous dissection in cervical arteries is 2.6 per 100,000 patients, and it constitutes 60% of all dissections. While the rate of spontaneous dissection in the internal carotid artery is 1.7: 100,000, it is 0.97: 100,000 in the vertebral artery.[4]

Neurological findings in dissection of the cervical arteries occur

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due to cerebral ischemia caused by thromboembolism, hypoperfusion or subarachnoid hemorrhage. In addition, cranial neuropathy, pain and Horner syndrome can be seen due to local nerve and vascular compression of the dissection.[5]

Intravenous thrombolytic therapy has been proven to be an effective and safe method in the treatment of acute ischemic stroke due to dissection, and it is applied safely.[6] It has been shown that mechanical thrombectomy in selected patients within the first 6 hours in major vessel occlusions of the anterior system circulation is a safe and effective method. However, our knowledge about the clinical results and reperfusion rates of endovascular treatment in patients with dissection is limited. In our study, we aimed to present our endovascular treatment experience in cervical artery dissections presenting with acute major vessel occlusion.

2. Materials and Methods

Patients who underwent endovascular treatment of acute ischemic stroke due to a major vessel occlusion secondary to extracranial or intracranial vessel dissection were extrapolated from Eskisehir Osmangazi Stroke Center Database between January 2015 and May 2020.

Age, gender, symptom time of all patients, time of admission to the emergency room, administration of thrombolytic therapy, demographic data, National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT (ASPECT) score, etiological diagnoses, mechanical thrombectomy method, recanalization rate, intracerebral hemorrhage rate (SITS-MOST), Modified Rankin Scale (mRS) score at discharge and 3 months later were recorded.

Baseine National Institute of Health Stroke Scale (NIHSS) of patients were recorded.

In Org 10172 in Acute Stroke (TOAST) classification, patients with ischemic stroke are classified in terms of etiology including large vessel atherosclerosis, cardioembolism, small vessel disease, stroke due to other etiological causes and stroke of unknown etiology.[7]

The patients were diagnosed as having dissection by computed tomography angiography (CT-A) (SIEMENS) imaging and digital subtraction angiography (PHILIPS ALLURA CLARITY).

Alberta Stroke Program Early CT (ASPECT) score is a scoring system in which ischemic areas in the brain tissue in the early period in acute ischemic strokes are evaluated and scored according to topographic classification. ASPECT score was recorded in each patient.[8]

In our protocol, thrombolytic therapy (tPA, alteplase) with a dose of 0.9 mg/kg was given in 60 minutes to the patients who were admitted within the first 4.5 hours after the onset of symptoms prior to mechanical thrombectomy. Patients presented after 4.5 hours of symptom onset were directly underwent mechanical thrombectomy. Patients who presented after 6 hours of symptom onset and patients with unknown stroke onset underwent CTP.

In the course of mechanical thrombectomy procedure; the guiding catheter type was chosen according to the anatomy of the common carotid artery. If the anatomy was good, the balloon guiding catheter was placed, if it is not good like elongation, tortuosity, and the presence of a loop, the guiding sheat was placed. If the dissecting segment was in the internal carotid artery, the occlusion site was reached by passing the dissecting segment with the help of a microwire and entering the true lumen. Middle cerebral artery or distal carotid artery occlusion was intervened with combined aspiration and stent retriever, isolated aspiration or isolated stenting. For basillary occlusion in vertebral V4 dissection, a long guiding sheath was placed in the V2 segment of the left vertebral artery. The lesion was passed under the leadership of microcatheter and microwire with a 6F aspiration catheter, and aspiration was performed with the ADAPT technique.

After mechanical thrombectomy, the evaluation of perfusion in the cerebral angiogram was made according to the Thrombolysis in Cerebral Infarction (TICI) scoring. The classification of post-procedure bleeding was made according to the Safe Implementation of Treatments in Stroke (SITS) Symptomatic Intracerebral Hemorrhage Risk Score.[9]

Ethics committee approval was obtained from Eskisehir Osmangazi University, Faculty of Medicine Ethics Committee for our study.

Table 1

Clinical characteristics of the patients

Mean age ± SD —year		43±9.84
Male gender — no (%)		6 (+46.1)
Medical history	Hypertension	3 (23%)
	Diabetes mellitus	1 (7%)
	Coronary artery disease	1 (7%)
	Atrial fibrillation	0
	Stroke in the past	1 (7%)
	Smoking	2 (15%)
Trauma history	Yes	2 (15%)
	No	11 (84.6%)
NIHSS score at admission	16.53	9-30
Median Systolic Blood Pressure- mm/Hg	144.84	100-180
Median Diastolic Blood Pressure- mm/Hg	88	60-106
Median Glucose Level - mg/dL	142	98-372

Table 2

Locations from where all the admitted patients were transferred

	N	%
Ambulance service	9	69
State hospitals (Eskisehir)	1	7
Bilecik	1	7
Kutahya	2	15
Total	13	100

3. Results

A total of 13 patients with a mean age of 43 ± 9.84 years were included in the study. Of the patients, 46.1% were male (n=6) and 53.8% were female (n=7). Ten of our patients presented within the first 6 hours, but the symptom onset time of 3 was unknown. In all 3 patients, the miss-match area was monitored by conventional CT-perfusion, and endovascular intervention was performed. Two patients had a history of blunt trauma within the last week. The average NIHSS score was 16.53 (9-30) at admission (Table 1). Of the patients, 69.2% (n = 9) were brought to the emergency room by the ambulance service (Table 2).

Figure 1

Hiperdens artery sign. A- Distal part of the internal carotid artery, B- Middle cerebral artery, C- Middle cerebral artery M2 segment (dot sign), D- Basilar artery

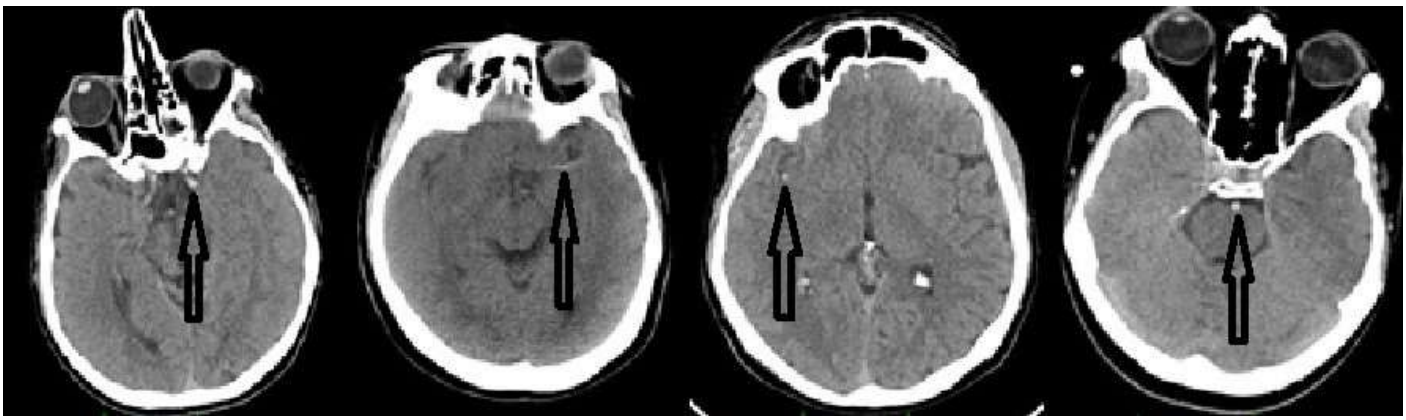
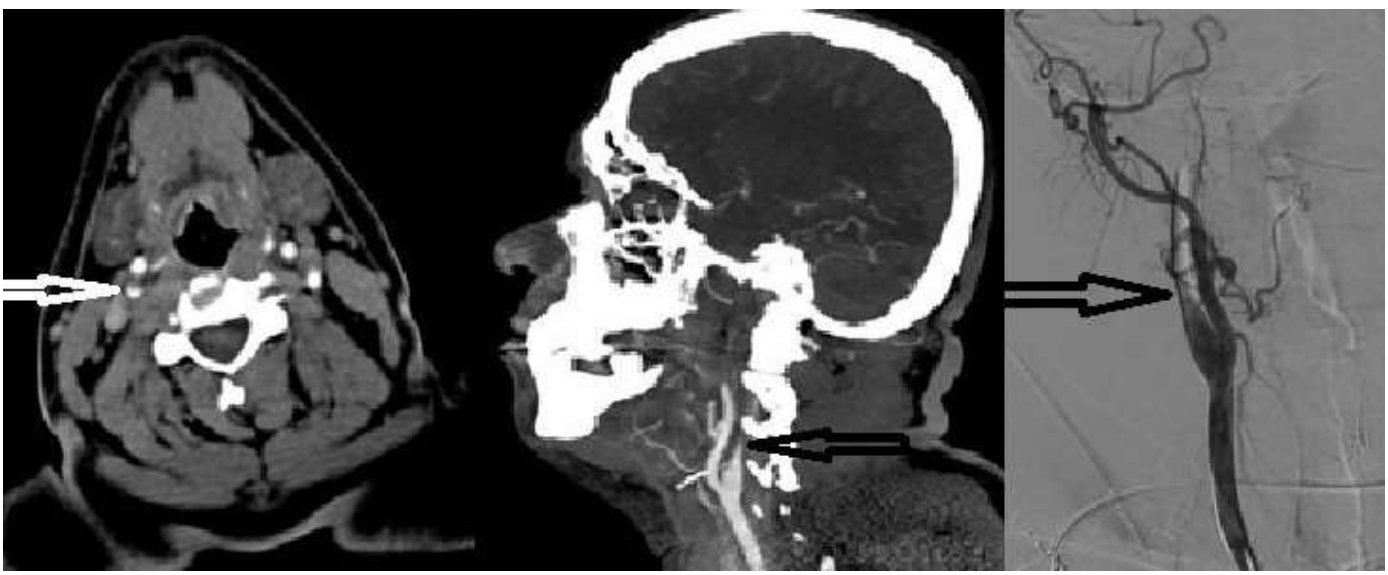


Figure 2

Dissection in axial (A) and sagittal (B) sections of CT- angiography and tandem occlusion in sagittal section; tandem occlusion in diagnostic angiography (C).



Mean symptom-to-door time was 104.63 ± 77.97 minutes (n = 13), and door-imaging time was 18.23 ± 15.87 minutes (n = 13). In the computerized tomography (CT), 92.3% of the patients had hyperdense artery sign (Table 3). In 15% of these patients, the hyperdens artery sign was observed in the distal part of the internal carotid artery (Figure 1A), in 69% in the middle cerebral artery (Figure 1B), in one patient in M2 segment of the middle cerebral artery (dot finding, Figure 1C) and in one patient in the basilar artery (Figure 1D) (Table 2).

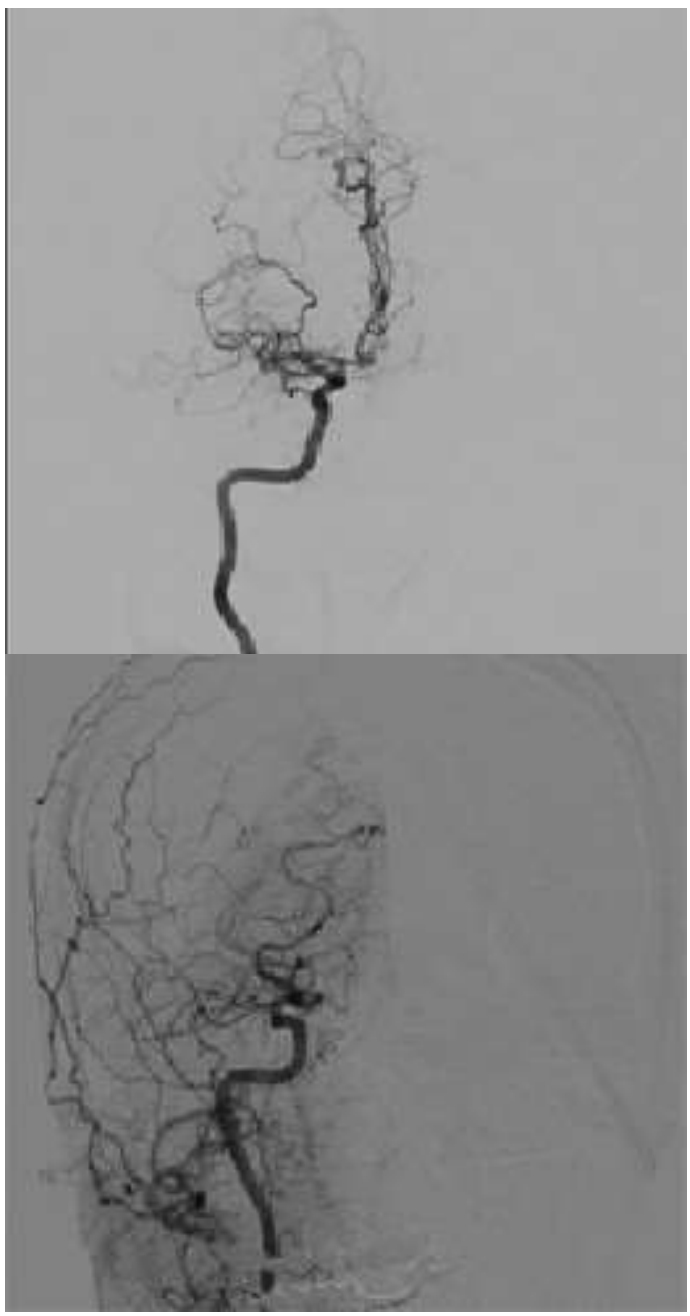
In diagnostic digital subtraction angiography (DSA) ,it was observed that 12 patients had internal carotid artery dissection (Table 4). Nine of the patients with internal carotid artery dissection had middle cerebral artery-internal carotid artery tandem occlusion (Figures 2A, 2B and 2C). In 2 of them the lumen was open even though the internal carotid artery was dissected and there was MCA M1 occlusion (Figure 3A). One patient had a dissected internal carotid artery in stenotic appearance and had a T occlusion (Figure 3B). One patient had vertebrobasilar occlusion due to dissection of V4 segment of vertebral artery (Figure 4). TPA was applied to 15% (n=2) of the patients. There were contraindications for tPA in 30% of the patients (n=4). Of the patients in whom tPA was contraindicated 50% (n=2) had wake-up stroke and one patient's symptom onset time was unknown. One patient had a history of major surgery in the last 3 months.

Fifteen percent of the patients (n=2) were taken to the neuroangiography unit after intubation. Femoral artery puncture was performed in all patients. Thromboaspiration method was applied in 46.1% of the patients (n=6) as the first technique in the procedure (Figure 4). Isolated stent was applied in 23% of the patients (n=3) as the first technique. Combined technique was applied in 30% (n=4) of the patients. First pass recanalization rate was found to be 38.4% (n=5). Two or more intracranial procedures had to be performed in 58.3% of the patients (n=7). Balloon angioplasty was performed in two patients (15%) as a salvage technique, and in two pa-

tients (15%) a permanent stent was placed in the internal carotid artery during the procedure. Ticagrelor was loaded as an antiaggregant in one patient, tirofibran bolus and infusion therapy was administered in one other patient.

Figure 3

MCA M1 occlusion (A), T occlusion and fetal PCA (B) in DSA



The time between the patient's admission to the emergency department and femoral artery puncture was 97.4 (38-201) minutes. The time between femoral artery puncture and recanalization was 18.23 (4-50) minutes. The rate of complete recanalization (TICI 2b-3) was 92.3% (n=12). Recanalization could not be achieved in one patient. First pass recanalization rate was 38.4% (n=5). Asymptomatic bleeding was observed in 23% (n=3) of the control CT imaging obtained 24 hours after thrombectomy. Two of the patients who had bleeding on CT had subarachnoid hemorrhage and one had type 2 petechial hemorrhage. Clinical progression and worsening of symptoms due to bleeding (NIHSS> 4) were not observed. One patient underwent decompressive hemicraniectomy due to a large hemispheric infarction on control CT imaging and died in postoperative follow-up.

At the end of the third month, 13 patients were evaluated in terms of being able to survive independently. The rate of patients who were living independently (mRS ≤2) was 76.9% (n=10).

Table 3

Hyperdense artery localizations

	n	%
Distal part of the internal carotid artery	2	15
Middle cerebral artery	8	61
Middle cerebral artery M2 segment (dot sign)	1	7
Basilar artery	1	7
Total	12	100

Table 4

Dissection and Occlusion Localizations

Internal Carotid Artery	ICA-MCA tandem	9 (69%)
	Distal ICA- T	1 (7%)
	MCA M1 segment	2 (15%)
Vertebral artery V4	Vertebrobasilar	1 (7%)

4. Discussion

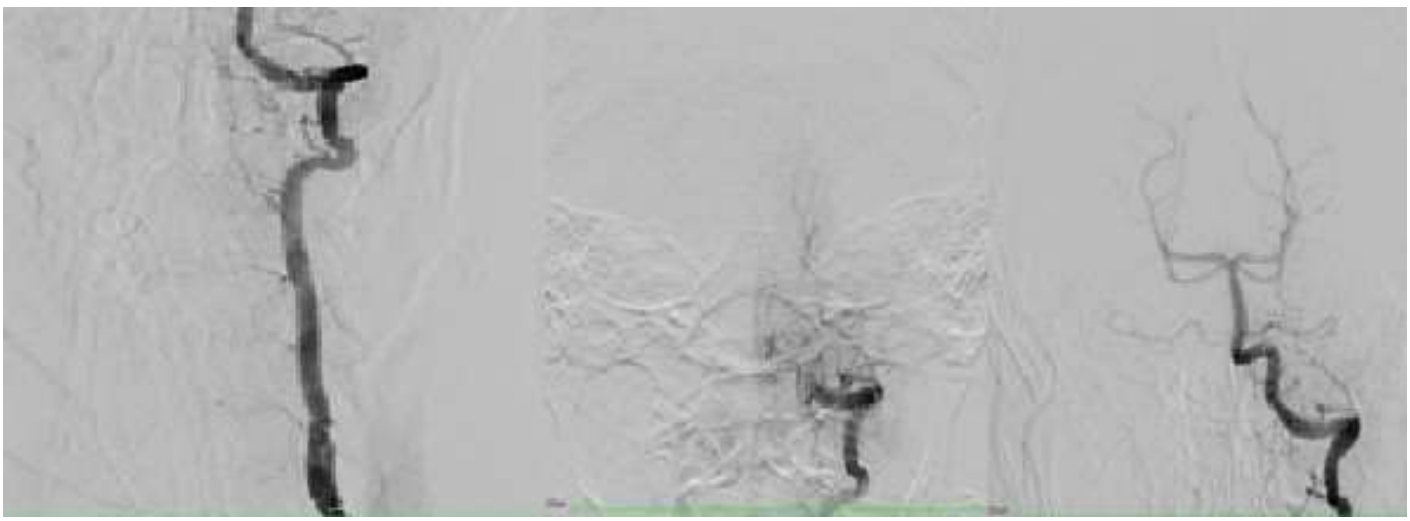
We retrospectively evaluated the data of 13 patients who were admitted to the emergency department of our hospital with major vessel occlusion between 2015 and 2020, who were treated with endovascular treatment (EVT), and whose etiology was dissection. The mean age of our patients was 43±9.84 years, and its frequency at a younger age was consistent with the literature. However, 53.8% of our patients were women and this result was different from previous epidemiological studies.[10]

In the study by Bogousslavsky et al. which was conducted in 1987, it was found that 23% of the patients with carotid dissection died within the first week, and 48% of them had poor functional recovery due to severe neurological deficit.[11] Thrombolytic therapy has been shown to be safe in dissection.[12,13] Nevertheless, although patients with dissection were younger and had less comorbidity, clinical deterioration was found to be higher compared to other patients treated with thrombolytic therapy.[14,15] This is thought to be because dissection patients mostly present with major vessel occlusion.

We selected our patients with computed tomography angiography (CT-A) imaging. However, since the last normal appearance time of our 3 patients was not known (2 patients with wake up stroke, the time in which the patient was last seen normal was unknown in 1 patient), we performed CT-perfusion imaging in these patients and decided for endovascular intervention because there was mismatch. DAWN and DEFUSE-3 showed that the appropriate time interval for mechanical thrombectomy was wider in appropriately selected patients.[16,17]

Figure 4

A 30-year-old female patient was brought in due to a change in consciousness that started 3 hours ago (NIHSS=30). Dissection of the vertebral artery (A) and proximal occlusion of the basilar artery were observed on angiographic imaging (B). Endovascular treatment was performed with the ADAPT technique, and TICI 3 (C) recanalization time was achieved after the procedure. Symptom to recanalization time was 325 min. Discharge mRS was 0.



In the study of Haussen et al., recanalization rate (TICI 2b-3 rate) was 95%. This rate was 92.3% in this study and it was similar to the literature.[18] First pass rate was 38.4% in recanalized patients. Asymptomatic bleeding was present in 23% of our patients. Although asymptomatic bleeding rate was 23%, good survival rate (mRS≤2) was found 76.9%. In the present study the good survival rate was high due to high rate of successful recanalization and the asymptomatic course of intracerebral bleeding.[18]

Since arterial dissections develop suddenly, there is less collateral circulation support in this group of patients compared to patients with occlusion in the atherosclerotic background. The inability of the collateral circulation to provide adequate perfusion support accelerates the transformation of the penumbra tissue into the infarct area.[19] However, although collateral circulation support is less in these patients, younger average age and lower vascular risk factors have a positive effect on good prognosis.[20]

During mechanical thrombectomy, we aimed primarily to open the occlusion in the intracranial segment from a technical point of view. This approach enabled us to achieve faster recanalization in intracranial occlusion without wasting time with revascularization of the internal carotid artery in the cervical segment. Providing early recanalization in intracranial occlusion ensured less final infarct tissue. In addition, dealing with the dissected internal carotid artery might cause re-embolism of new thrombus tissue.[21]

An adjuvant procedure to the internal carotid artery was performed in 4 of our patients during acute procedure. Balloon angioplasty was applied in 2 patients, and self-expandable stent was applied in 2 patients. Ticagrelor was loaded in 1 of the patients we acutely stented, and tirofiban was loaded and then given as infusion in the other patient we acutely stented. In 1 of our patients, the stent was occluded in the acute period, but clinical progression was not observed in the patient. Asymptomatic or symptomatic bleeding was not observed in the control CT imaging in both patients. A total of 15.3% (n=2) of the patients were stented during the acute procedure, and stent was observed to be occluded in 1 patient. A self expandable stent was placed in the carotid artery in 1 of our patients under clopidogrel treatment one week after the incident.

After revascularization was achieved in the intracranial artery occlusion, we did not stent immediately if the internal carotid artery was not opened in the first stage imaging. We were very selective in terms of internal carotid artery stenting, because the dissection in the internal carotid artery could spontaneously resolve, and the implanted stent could be occluded due to increased thrombogenicity in the acute period. After washing with fluid for a while, we punctured the contralateral femoral artery in patients with no flow in the ipsilateral internal carotid artery. In the imaging taken from the contralateral common carotid artery, we terminated our procedure at this stage if flow was observed on the occlusion side via the anterior communicating artery. Collateral circulation support is insufficient in patients with dissection since the event is acute. However, the Willis polygon works better because dissection is seen in a relatively younger patient population.[22] In such patients, it is important to learn that the anterior communicating artery is working and that the middle cerebral artery is filling from the contralateral internal carotid artery by taking images from the opposite common carotid artery. For this reason, it is advantageous to use both groins, to perform a procedure with one groin and to get an image from the other groin. After the middle cerebral artery is fully recanalized, the dissected internal carotid artery can be left occluded without stenting, if there is a passage through the anterior communicant artery from the unaffected internal carotid artery. However, if the communicant arteries are insufficient or hypoplastic, stenting decision can be taken in patients who are suitable for.

The mortality in acute basilar artery occlusion is between 75-91%, and survivors rarely regain functional independence.[23,24] Although recanalization rates are good with thrombolytic therapy, the mortality rate has only decreased to 65-75%. This situation has necessitated different treatment approaches.[25] The most common cause of acute basilar artery dissection in young patients is traumatic vertebral artery dissection.[26] The treatment approach is rescue therapy (first thrombolytic therapy followed by mechanical thrombectomy) and does not have a high level of evidence. Although it may vary depending on the location of the clinical occlusion and

collateral circulation support, it generally has a poor prognosis. Our patient was a 30-year-old woman and a boxer. In the emergency department, Glasgow Coma Score (GCS) was 3, there was basilar artery occlusion in CT-A imaging. Recanalization was achieved with the thromboaspiration technique in the patient who underwent mechanical thrombectomy and she was discharged without any sequelae in the postoperative period. Vertebral artery dissections are frequently seen in the V2-V3 segments. But in our patient, the V4 segment was occluded. Occlusion of the V4 segment did not cause prolongation in our procedure.

Our study had limitations due to its single center, retrospective non-randomized-controlled design and small sample size.

5. Conclusion

Endovascular treatment of acute ischemic stroke due to dissection is effective and safe. Dissection has an important place in the etiology of young patients presenting with ischemic stroke. In patients with major vascular occlusions, this etiology should be kept in the foreground, and mechanical thrombectomy should be applied in appropriate centers along with thrombolytic therapy. It is necessary to decide on the endovascular technique to be applied on a patient basis.

Statement of ethics

Ethics committee approval was obtained from Eskisehir Osmangazi University, Faculty of Medicine Ethics Committee for our study. (E-25403353-050.99-182189 -11)

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers. This manuscript has been presented orally in 56. National Neurology Congress, 16-21 November, 2019. This study was re-evaluated by adding new patients after the presentation.

Author contributions

FAK: Draft of manuscript, Data collection, Statistical analysis, ZUK: Data collection, Tables, ÖK: Graphic design, supervision, AÖÖ: Conception and design of the manuscript, supervision, review. All authors read and approved the final version of the manuscript.

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Impact of Intraoperative End-Tidal CO_2 Variations on Postoperative Nausea, Vomiting, and Pain

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Abstract

Aim: Patients undergoing robotic-assisted laparoscopic procedures tend to experience a higher frequency of postoperative nausea and vomiting (PONV). This study aimed explore the influence of intraoperative end-tidal carbon dioxide ($ETCO_2$) levels on the occurrence of PONV in robotic surgery.

Methods: This observational clinical study included patients undergoing robotic laparoscopic radical prostatectomy. Patients were divided into two groups based on intraoperative $ETCO_2$ levels: Group 1 (26–35 mmHg) and Group 2 (36–45 mmHg). The incidence of PONV, the use of rescue antiemetics, and pain scores were recorded at 0, 2, 4, 8, 12, and 24 hours postoperatively.

Results: We found that Group 1 exhibited lower PONV scores at both 0 ($p < 0.001$) and 2 ($p = 0.046$) hours post-surgery. Furthermore, Group 2 had a higher incidence of PONV and greater usage of rescue antiemetics within the first 24 hours following surgery. ($p<0.05$)

Conclusions: We found that lower intraoperative $ETCO_2$ levels were associated with a reduced incidence of PONV in robotic laparoscopic surgery, a procedure known to carry a high risk of PONV. PONV remains a significant clinical issue that negatively affects patient comfort and recovery. We believe that future research should continue to explore the effectiveness of both pharmacological and non-pharmacological approaches for the prevention of PONV.

Keywords: *End-tidal carbon dioxide; Pain; Postoperative nausea and vomiting; Robotic-assisted laparoscopic radical prostatectomy*

1. Introduction

Radical prostatectomy remains a cornerstone surgical intervention for managing prostate cancer and may be carried out via open, laparoscopic, or robot-assisted approaches. Among these, robotic-assisted surgery provides distinct benefits such as tremor filtration and improved dexterity, which together help minimize intraoperative bleeding. Moreover, robotic surgery has been associated with faster return to daily activities and shorter hospital stays for patients.[1-3]

This surgery is performed in the Trendelenburg position, a head-down posture, combined with intraperitoneal carbon dioxide (CO_2) insufflation. In addition to increased intra-abdominal pressure, this technique leads to elevated intracranial and intraocular pressures due to the Trendelenburg positioning and pneumoperitoneum. Moreover, patients undergoing robotic-assisted laparoscopic procedures tend to experience a higher frequency of postoperative nausea and vomiting (PONV).[4,5] PONV can lead to dehydration, electrolyte imbalances, extended hospitalizations.[6]

The chemoreceptor trigger zone (CTZ), which is responsible for triggering the vomiting reflex, is situated outside the blood-brain barrier. Various mediators, including histamine, serotonin, neurokinin-1, and dopamine, are involved in pathophysiology of nausea and vomiting. While the precise mechanism underlying PONV is not fully understood, it has been reported that tissue hypoxia in the brain and gastrointestinal tract may stimulate the vomiting center. In laparoscopic surgeries, CO_2 insufflation due to pneumoperitoneum can increase intracranial pressure, which may in turn elevate the incidence of PONV.[7,8] Several studies have investigated the impact of varying intraoperative end-tidal carbon dioxide ($ETCO_2$) levels on occurrence of PONV. However, current literature presents inconsistent findings regarding the relationship between different $ETCO_2$ levels and PONV incidence.[9,10]

This study aimed explore the influence of intraoperative $ETCO_2$ levels on the occurrence of PONV. The primary goal was to evaluate the incidence of PONV, with secondary aims focusing on the use of antiemetic and postoperative pain assessment.

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2. Materials and Methods

This observational clinical study included patients undergoing robotic laparoscopic radical prostatectomy. (Ethics No: 102; Date: 26/04/2023). Exclusion criteria included: refusal to participate, age under 18, history of PONV, motion sickness, abnormal fluid-electrolyte balance, hepatic or renal failure, and current use of steroids or antiemetic medications.

Patients were divided into two groups based on intraoperative $ETCO_2$ levels: Group 1; 26–35 mmHg, and Group 2: 36–45 mmHg.[9]

All patients received an identical anesthetic protocol for induction. For maintenance of anesthesia, 0.8–1.2 MAC sevoflurane and remifentanil at 0.05–0.2 mcg/kg/min were administered. Intraoperative ventilation was managed using a volume-controlled ventilation mode with 50% oxygen and 50% air, a tidal volume of 6 mL/kg, and a respiratory rate of 12 breaths per minute. Standard intraoperative monitoring included heart rate, noninvasive blood pressure, pulse oximetry (SpO_2), $ETCO_2$, bispectral index (BIS), temperature, urine output. All patients received 100 mg intravenous tramadol, 1 g paracetamol for analgesia, and 4 mg ondansetron as an antiemetic. During the first 24 hours postoperatively, all patients routinely received 100 mg intravenous tramadol and 1 g paracetamol for pain control.

PONV score and antiemetic requirements were assessed using the Verbal Descriptive Scale (VDS). (0-2-4-8-12-24 hours).[11] Individuals with an VDS of ≥2 received 4 mg ondansetron. VDS:

0=no PONV: patient reports no nausea and has had no emesis episodes;

1=mild PONV: patient reports nausea but declines antiemetic treatment;

2=moderate PONV: patient reports nausea and accepts antiemetic treatment;

3=severe PONV: nausea with any emesis episode (retching or vomiting).

Pain was assessed using the Numerical Rating Scale (NRS). Individuals with an NRS score greater than 4 were administered 50 mg dexketoprofen as rescue analgesia.

2.1. Statistical analysis

According to the results of a preliminary study in which the incidence of PONV was closed to 50%, 46 patients were required for each group to detect 40% reduction in the incidence of PONV (a=0.05, b=0.20). So 56 patients were enrolled for possible dropouts in each groups. The numerical values were expressed as the mean ± standard deviation or median (range). The Chi-square test (for categorical variables), One-way ANOVA (for continuous variables with normal distribution), and Mann-Whitney U tests (for continuous variables with non-normal distribution) were employed in this study.

3. Results

A total of 112 patients who underwent robot-assisted laparoscopic radical prostatectomy were initially enrolled in the study. However, two patients were excluded due to conversion to laparotomy during the intraoperative period, and one patient was excluded due to reoperation in the postoperative period. As a result, the final analysis included 109 patients.(Figure 1). The demographic and clinical features were similar between the two groups.(Table 1).

At postoperative hour 0, the PONV score distribution (0/1/2/3) was 46/6/2/0 in Group 1 and 26/21/8/0 in Group 2 ($p < 0.001$). At postoperative hour 2, the PONV score distribution (0/1/2/3) was 44/7/3/0 in Group 1 and 33/14/8/0 in Group 2 ($p = 0.046$).(Table 2)

Figure 1

Flow diagram of the study

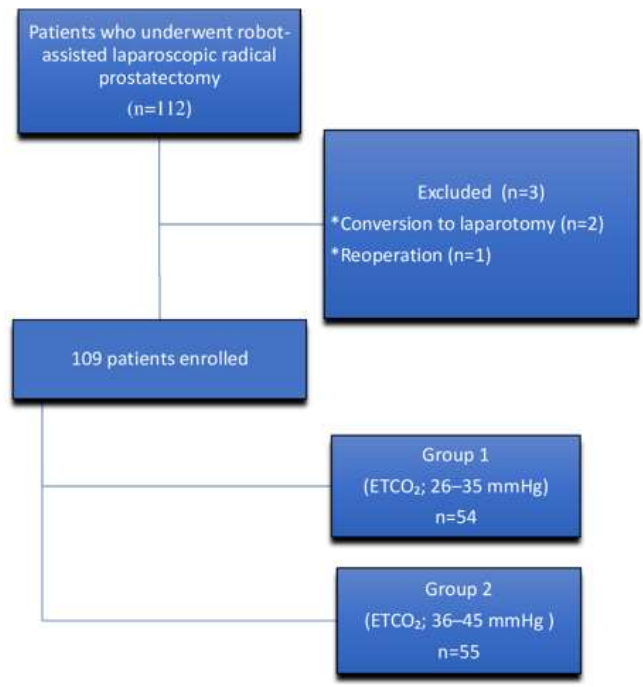

Table 1

Clinical characteristics of the patients

	Group 1 n=54	Group 2 n=55	p
Age (year)	63.63 ± 6.91	63.40 ± 5.79	0.851
BMI (kg/m^2)	27.36 ± 4.42	26.58 ± 2.77	0.273
ASA Score (2/3) (n)	38/16	43/12	0.351
Duration of surgery (minute)	233.79 ± 32.15	226.73 ± 32.74	0.258
Comorbidities			
· Hypertension	22	19	0.504
· Diabetes mellitus	18	17	0.786
· CAD	16	10	0.161
· COPD	5	7	0.563
· Smoking	12	15	0.541

Values are presented as Mean ± SD and numbers. n: Number, BMI: Body Mass Index, ASA: American Society of Anesthesiologists, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease.

PONV scores at 4, 8, 12, and 24 hours postoperatively were similar between the two groups ($p > 0.05$).(Table 2)

PONV occurred within the first 24 hours postoperatively in 17 patients (31.4%) in Group 1 and in 29 patients (52.7%) in Group 2 ($p = 0.025$) Rescue antiemetic therapy was required in 5 patients in Group 1 and 14 patients in Group 2 ($p = 0.026$).(Table 2)

Postoperative pain scores assessed by the Numerical Rating Scale (NRS) at all time points were comparable between the two groups ($p > 0.05$) (Table 3).

Table 2

PONV Incidence and Severity

	Group 1 n=54	Group 2 n=55	p
PONV(n, %)	17 (31.4)	29 (52.7)	0.025*
PONV Score (n) 0/1/2/3			
0th hour	46/6/2/0	26/21/8/0	<0.001*
2nd hour	44/7/3/0	33/14/8/0	0.046*
4th hour	52/2/0/0	51/3/1/0	0.549
8th hour	51/3/0/0	51/1/3/0	0.136
12th hour	53/1/0/0	53/2/0/0	0.569
24th hour	54/0/0/0	54/1/0/0	0.320
Required antiemetic (n)	5	14	0.026*

*Values are presented as numbers. n: Number/Percentages, PONV: postoperative nausea and vomiting. p<0.05 was considered significant. *: There were significant differences between the two groups.*

Table 3

Pain scores (NRS)

	Group 1 n=54	Group 2 n=55	p
NRS 0th	5(4)	4(4)	0.207
NRS 2th	3(4)	3(2)	0.414
NRS 4th	3(3)	2(4)	0.374
NRS 8th	2(2)	2(3)	0.469
NRS 12th	2(4)	2(4)	0.929
NRS 24th	2(3)	2(3)	0.259

NRS: Numeric Rating Score. Values are given as median (range) and numbers. p<0.05 was considered significant.

4. Discussion

In this study, which examined the the effects of $ETCO_2$ variations on PONV, we found that Group 1 exhibited lower PONV scores at both 0 and 2-hours post-surgery. Furthermore, Group 2 had a higher incidence of PONV and greater usage of rescue antiemetics within the first 24 hours following surgery.

In a study by Son et al. [12], which examined different $ETCO_2$ levels (36–40 mmHg, 41–45 mmHg, and 46–50 mmHg) and PONV, it was reported that PONV incidence and the use of antiemetics were similar across all groups. In contrast, Feng et al. [13] reported a higher incidence of PONV in the hypercapnic group among patients undergoing thyroidectomy. Similarly, a study conducted in laparoscopic gynecological surgeries found a higher PONV incidence associated with elevated $ETCO_2$ levels. That study also reported a greater increase in optic nerve sheath diameter (ONSD) in the hypercapnic group compared to the normocapnic group following pneumoperitoneum.[9] Yılmaz et al. [14] also reported that in patients undergoing laparoscopic hysterectomy, those who experienced an increase in ONSD due to Trendelenburg positioning and pneumoperitoneum had a higher incidence of PONV. In accordance with the existing literature, our study found that Group 1 had a lower incidence of PONV and required less antiemetic. In the study by Son et al. [12], all $ETCO_2$ values were above 36 mmHg. In our study, we compared patients in Group 1 (26–35 mmHg) with those in Group 2 (36–45 mmHg). We believe the difference between our results and those of Son et al. may be due to the differing ranges of $ETCO_2$ values evaluated.

In another study investigating the effect of $ETCO_2$ levels (31–33 mmHg, 37–39 mmHg, and 43–45 mmHg) on PONV during percutaneous nephrolithotomy, patients with higher $ETCO_2$ levels were found to have a lower incidence of PONV than those in the other two groups, between which the incidence was similar.[15] Fujimoto et al.[10] reported that, in open gynecological surgeries, patients with $ETCO_2$ levels below 31 mmHg had a higher incidence of PONV compared to those with values above 35 mmHg. In contrast to these studies, our patient cohort consisted exclusively of those undergoing robot-assisted laparoscopic radical prostatectomy, which involves Trendelenburg positioning and intraperitoneal CO_2 insufflation. We believe the differences in surgical technique may account for the discrepancies in findings. Moreover, in the study by Fujimoto et al.[10], three different anesthetic agents—sevoflurane, desflurane, and propofol—were used for maintenance of anesthesia, which may also have influenced the outcomes.

It has been proposed that the rise in intra-abdominal pressure during laparoscopic surgery disrupts venous drainage from lumbar plexus by compressing inferior vena cava.[16] Moreover, the increased intra-abdominal pressure elevates diaphragm, leading higher intrathoracic pressure, which in turn hinders right atrial and ventricular filling and obstructs superior vena cava drainage. This increase in central venous pressure, coupled with the reduced venous return from lumbar plexus and central nervous system, is believed to play role in observed elevation of intracranial pressure (ICP) during laparoscopic procedures.[17,18] The resultant circulatory disturbances can lead to the release of mediators such as histamine and serotonin. Furthermore, serotonin release has also been reported following intestinal ischemia and reperfusion [8, 19]. Collectively, these mechanisms are thought to contribute to the increased incidence of PONV observed after laparoscopic surgeries. In our study, we believe these mechanisms played a role in the higher incidence of PONV observed in Group 2.

4.1. Limitations

This study has several limitations. First, we did not directly monitor patients using intracranial pressure (ICP) or intra-abdominal pressure (IAP) measurements. Second, the follow-up period was limited to 24 hours postoperatively, so we were unable to assess long-term outcomes in our patient population.

5. Conclusion

Despite the numerous advantages of robotic laparoscopic surgeries, they are associated with a risk of PONV. In this study, we found that lower intraoperative $ETCO_2$ levels were associated with a reduced incidence of PONV. PONV can develop due to various factors related to anesthesia, medications used, patient characteristics, and the surgical procedure itself. Particularly common in laparoscopic surgeries, PONV remains a significant clinical issue that negatively affects patient comfort and recovery. Therefore, we believe that future research should continue to explore the effectiveness of both pharmacological and non-pharmacological approaches for the prevention of PONV.

Statement of ethics

Ethics committee approval was obtained from Ankara Etlik City Hospital Ethics Committee for our study. (Ethics No: 102; Date: 26/04/2023)

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

YO: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, visualization, writing–original draft, writing–review & editing. DG: Conceptualization, data curation, investigation, methodology, visualization, writing–original draft, writing–review & editing. CKÇ: Conceptualization, formal analysis, methodology, project administration, resources, supervision, visualization, writing–review & editing. EEH: Conceptualization, investigation, methodology, project administration, supervision, visualization, writing–review & editing. SA: Conceptualization, formal analysis, methodology, visualization. JE: Conceptualization, methodology, project administration, resources, supervision, writing–review & editing. All authors read and approved the final version of the manuscript.

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Granisetron's Preemptive Effect on Hemodynamic Changes in General Anesthesia During Laparoscopic Cholecystectomy

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Abstract

Aim: Laparoscopic cholecystectomy causes hemodynamic changes such as decreasing preload, compression on vena cava inferior. These effects are correlated with increased intraabdominal pressure due to pneumoperitoneum. This study aims to evaluate the effect of granisetron (1 mg) in the prevention of post-induction hypotension in adult patients with laparoscopic cholecystectomy under general anesthesia.

Methods: One hundred and forty American Society of Anesthesiologists (ASA) status I-II patients, aged 18 to 65 years, undergoing elective laparoscopic cholecystectomy surgery under general anesthesia were included. Mean blood pressure (MBP), heart rate (HR) and are measured and recorded 1 minute after induction, 1 minute before intubation, 1 minute after intubation and every 5 minutes during operation. Intubation quality was assessed by Evans score at one minute after intubation.

Results: The demographic variables (gender, age, weight, height and body mass index (BMI)) were similar in both groups. The mean blood pressure was decreased in 22 patients (%31.4) in saline group (Group S) and 8 patients (%11.4) in granisetron group (Group G) compared to baseline values after 15 minutes of granisetron administration at reverse Trendelenburg position. At the same period, the heart rate was decreased in 12 patients (%17.1) in group G 18 patients (%25.7) in group S

Conclusions: Granisetron prevented hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute of granisetron administration. It can be used safely in adult patients and patients having risks of hypotension due to positions during general anesthesia.

Keywords: *Granisetron; hypotension; general anesthesia; propofol; laparoscopic cholecystectomy*

1. Introduction

Propofol is the most commonly used intravenous anesthetic agent for daily anesthesia due to its soft induction and fast recovery properties.[1] However, hypotension that occurs in induction is the most common disadvantage. The hypotensive effect of propofol was attributed to a combination of venous and arterial vasodilatation, a decrease in systemic vascular resistance and/or cardiac output, which was due to impairment of the baroreceptor reflex mechanism and depression of myocardial contractility.[2]

Preemptive treatments play a critical role in mitigating the hemodynamic side effects of anesthesia. Various strategies have been employed to prevent hypotension, including the administration of volume expanders, physical methods to enhance venous return, and the use of vasopressors 5-HT3 antagonists are primarily used to prevent postoperative nausea and vomiting (PONV).[3] Granisetron, a selective 5-HT3 receptor antagonist, belongs to this class. Ondansetron, another 5-HT3 antagonist, has been shown to be effective in preventing hypotension following both spinal and general anesthesia.[4] The Bezold-Jarisch reflex, which contributes to systemic hypotension, bradycardia, and vasodilation, is mediated by mechanoreceptors and serotonin-sensitive chemoreceptors located in the heart wall.[5] Serotonin is thought to play a central role in triggering this reflex, particularly in the context of post-spinal anesthesia-induced hypotension.

Laparoscopic cholecystectomy has become the gold standard for cholelithiasis and it's performed under general anesthesia. Laparoscopic cholecystectomy causes hemodynamic changes such as de-

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creasing preload, compression on vena cava inferior. These effects are correlated with increased intraabdominal pressure due to pneumoperitoneum.[6,7]

The primary aim of this study is conducted to determine the effectiveness of granisetron (1 mg) in the prevention of post-induction hypotension in adult patients with laparoscopic cholecystectomy under general anesthesia. Secondary aims were to evaluate the incidence of bradycardia and hypotension during the surgery.

2. Materials and Methods

Institutional Ethics Committee approval and written informed consent (Ref no 28/19, 04/04/2016) were obtained, and the study was registered in clinicaltrials.gov (NCT03180229). One hundred and forty American Society of Anesthesiologists (ASA) status I–II patients, aged 18 to 65 years, undergoing elective laparoscopic cholecystectomy surgery under general anesthesia was randomly allocated to two groups with sealed envelope technique. Patients with a history of hypertension, cardiorespiratory diseases, renal disorders, acute pancreatitis, cognitive disorders or which are using antihypertension medication and who written informed consent could not be obtained were excluded from the study. On the other hand, patients who have passed to open surgical intervention were excluded.

Peripheral venous catheterizations of patients were performed with 20-gauge needles and Ringer lactate (2 ml/kg) was administered before operation during the fasting period. Standard monitorization and BIS (BIS Quatro sensor and BIS VISTA monitor) were administered to all patients. After recording baseline heart rate and blood pressure, patients were randomly divided into two groups.

Group G (n=70) received 1 mg granisetron (KYTRİL® 3 mg / 3 mL, i.v. Assos Medical, Türkiye) diluted in 5 ml of saline and group S (n= 70) received 5 ml of saline before 5 minutes from anesthesia induction. Patients in both groups did not receive any premedication. Anesthesia was induced with propofol 2.5 mg/kg. i.v. mean blood pressure (MBP), heart rate (HR) and are measured and recorded 1 minute after induction, 1 minute before intubation, 1 minute after intubation and every 5 minutes during operation. All patients received fentanyl 1 µg/kg and rocuronium 0.8 mg/kg as neuromuscular blockade before intubation. Anesthesia was maintained using sevoflurane at 1 to 1.2 minimum alveolar concentrations with fractional inspired oxygen of 0.5. Controlled ventilation continued with a rate of 10-14 breath/min and a tidal volume of 6-10 ml/kg aiming for an end-tidal carbon dioxide (EtCO2) of 35-40 mmHg without positive end Expiratory Pressure (PEEP). Maintenance fluid of ringer lactate was infused at 5-10 ml/kg/h during operation in both groups. At the end of the surgery, neuromuscular blockade was antagonized with 0.01 mg/kg atropine and 0.03-0.05 mg/kg neostigmine. Tramadol 100 mg iv infusion was administered approximately 15 minutes before the end of surgery for postoperative analgesic treatment. All patients received dexketoprophen trometamol 25 mg (3×1) on the postoperative first day. When patients complained of pain, was administered intravenous tramadol (100 mg) as a rescue analgesic.

The primary outcome variable in this study was proportions of patients with marked hypotension defined as mean arterial blood pressure (MAP) at least 25% less than the basal value at any time during the procedure. If hypotension occurred vasopressors (5 mg doses of ephedrine) treatments were administered. Bradycardia was defined as heart rate below 60 or %25 dropped. Intubation quality was assessed by Evans score at one minute after intubation (Table 1). The patients were observed in the Post Anesthesia Care Unit for 30 minutes and then transferred to their ward.

2.1. Statistical methods

According to the results of a previous study in which the incidence of hypotension following induction was closed to 45%, 65 patients were required for each group to detect a 50% reduction in the incidence of hypotension (α= 0.05, β = 0.20). So, 75 patients were enrolled for possible dropouts in each group (4). Statistical Package for Social Sciences (SPSS) software (version 22.0, SPSS, Inc, Chicago, IL, USA) was used for the statistical analysis. Numerical variables were summarized with mean ± standard deviations. Qualitative variables were expressed as numbers and percentages. Differences in numerical variables among the groups and intra-groups were examined by a t-test in independent groups. Differences in quality variables in ASA status between groups were examined using the chi-square test. Differences in MBP and HR within and between groups were investigated by repeated measures of variance analysis and student t test. The statistical significance level was considered $p < 0.05$.

Table 1

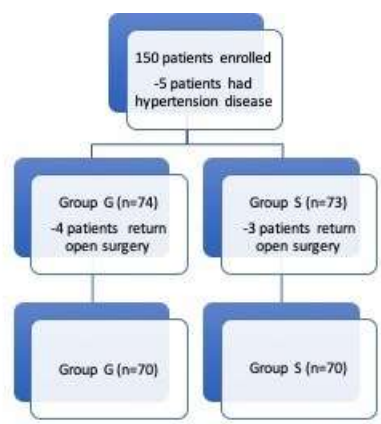
Evans (PRST) score

Systolic blood pressure	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Heart rate	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Sweating	No	0
	Moist skin	1
	Visible skin	2
Tears	No	0
	Yes	1
	Overflowing	2

Evans scores parameters determine the total score which can range from 0 to 8. Inadequate depth of anesthesia is scored as more than three. PRST: pressure, rate, sweating, tears

Figure 1

Flowchart



Group G: Granisetron group, Group S: Saline group

3. Results

One hundred fifty patients were enrolled to study. Four patients in group G and 3 patients in group S were returned to open surgery and excluded from the study. One patient in group G and 2 patients in group S had hypertension disease and they excluded from the study. One hundred forty patients were analyzed finally (Figure 1).

The demographic variables (gender, age, weight, height and body mass index (BMI)) were similar in both groups (Table 2) (p>0.05). The baseline blood pressure measurements were demonstrated in table 2 (p>0.05). The MAP and HR reduced after induction in both groups but there were no differences between groups (p>0.05). The mean blood pressure was decreased in 22 patients (%31.4) in group S and 8 patients (%11.4) in group G compared to baseline values after 15 minutes of granisetron administration (p <0.05) at reverse Trendelenburg position (Table 3). At the same period, the heart rate was decreased in 12 patients (%17.1) in group G 18 patients (%25.7) in group S (p<0.05) (Table 3). Although granisetron group was more stable and closer to baseline hemodynamic variables than the control group, there was no statistically significant difference in hemodynamic variables (MBP and HR) between the groups in other measurement times (p> 0.05) (Figure 2&3). Both groups were similar in respect to Evans Score (p>0.05) (Table 1).

Table 2

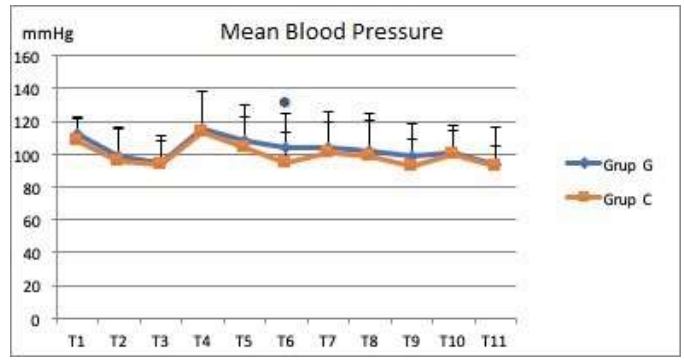
Demographic data

		Group S (n=70)	Group G (n=70)	p
ASA (n, %)	I	34 (%48.6)	35 (%50)	0.866
	II	36 (%51.4)	35 (%50)	
Gender (n, %)	Male	51 (%72.9)	48 (%68.6)	0.710
	Female	19 (%27.1)	22 (%31.4)	
Length (cm) (mean±SD)		168.8±9.5	168.5±8.3	0.821
Weight (kg) (mean±SD)		77.0±11.4	78.6±12.0	0.424
Age (yr) (mean±SD)		47.5±14.9	51.2±11.2	0.099
BMI (kg/m^2) (mean±SD)		27.2±4.6	27.8±4.3	0.491
Evans (PRST) score (mean±SD)		1.64±1.38	1.57 ±1.35	0.758
Systolic blood pressure (mmHg)		147.7±15.7	144.9±18.2	0.413
Diastolic blood pressure (mmHg)		87.4±9.9	84.4±11.4	0.146
Mean blood pressure (mmHg)		112.7±10.2	108.5±13.5	0.076

ASA: American Society of Anesthesiologists Status, BMI: Body mass index, PRST: pressure, rate, sweating, tears

Figure 2

Mean Blood Pressure



*Group G: Granisetron group, Group S: Saline group, T1: one minute before induction, T2: one minute after induction, T3: one minute before entubation, T4: one minute after entubation, T5: 10 minutes of granisetron administration, T6: 15 minutes of granisetron administration, T7: 20 minutes of granisetron administration, T8: 25 minutes of granisetron administration, T9: 30 minutes of granisetron administration, T10: 35 minutes of granisetron administration, T11: 40 minutes of granisetron administration, * p<0.05 between two groups*

Figure 3

Heart Rate

*Group G: Granisetron group, Group S: Saline group, T1: one minute before induction, T2: one minute after induction, T3: one minute before entubation, T4: one minute after entubation, T5: 10 minutes of granisetron administration, T6: 15 minutes of granisetron administration, T7: 20 minutes of granisetron administration, T8: 25 minutes of granisetron administration, T9: 30 minutes of granisetron administration, T10: 35 minutes of granisetron administration, T11: 40 minutes of granisetron administration, * p<0.05 between two groups*

Table 3

Patients data with hypotension and bradycardia

	Group G (n=70)	Group S (n=70)	p
T2 (n, %)			
· Hypotension	25 (35.7)	26 (37.1)	0.984
· Bradycardia	20 (28.5)	19 (27.1)	0.986
T6 (n, %)			
· Hypotension	8 (11.4)	22 (31.4)	0.001
· Bradycardia	10 (14.2)	21 (30)	0.025

T2: one minute after induction, T6: 15 minutes of granisetron administration

4. Discussion

This study showed that administrating preemptive granisetron couldn't prevent the incidence of hypotension after anesthesia induction in adult patients. But it prevented the incidence of hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute after granisetron administration. On the other hand, we observed a more stable and closer to baseline hemodynamic variables in granisetron group than the saline group. As far as we are concerned, this may be the first study administering preemptive granisetron in adult patients for preventing hypotension under general anesthesia.

Hypotension occurs generally both during spinal and general anesthesia. Both the intravenous and inhalations anesthetics cause hypotension during in general anesthesia. Also in this study, we used propofol for induction and sevoflurane for maintenance of anesthesia. They were decreased the systemic vascular resistance and cardiac output. In spinal anesthesia venous return, cardiac output, and systemic vascular resistance were decreased and this was the main mechanism of hypotension.[8] Bradycardia and hypotension from stimulation of cardiac chemoreceptor and mechanoreceptor were established.[9] Spinal anesthesia-related triggering of BJR is known to result from stimulation of 5-HT3 receptors in vagal nerve endings.[10,11] In the previous study showed that the effects of serotonin administration on systemic hemodynamics variable on rabbits. It revealed that hypotension and bradycardia similar to that associated with BJR occurred. 5-HT3 receptors have been associated with anxiety, vomiting, and stress-induced gastrointestinal problems. Another study showed that granisetron was significantly prevented paradoxical bradycardia and reduce the systolic blood pressure (SBP) due to bleeding.[12] So, in this study, we observed that more bradycardia in group S after reverse Trendelenburg position with CO_2 insufflation in 15th minute of granisetron administration. We thought that this could be as the same mechanism (5HT3 receptor blockade inhibited the vagal reflex) of the previous studies.

When serotonin is administered iv, vasoconstriction and consequent increase in preload cause blood pressure elevation. Golparvar et al.[4] have shown that ondansetron used before induction in an elderly patient population is effective in prevented post-induction hypotension but no effects on heart rate. They used ondansetron 20 minutes before induction. Granisetron's peak onset time is 3-5 minute after iv. administration and hypotension caused by propofol have a peak effect after 1-3 minutes of induction. For this reason, we administered granisetron which was another 5HT3 antagonist, five minutes before induction but did not find any effect on post-induction hypotension. There is no study for the best time interval for granisetron administration for prevention of post-induction hypotension. Also, elderly people have different hemodynamic variable than adults. In our study, we included adult patients (18-65yr) as the elderly population lacks dramatic response to hypotension. So, we didn't observe any changes in this period in both groups. The depth of anesthesia is a common reason for hemodynamic changes due to laryngoscopy. The high level of serotonin may play a role in this effect. PRST score (pressure, rate, sweating, tears) was defined by Evans and proposed for the detection of inadequate depth of anesthesia. Evans scores parameters determine the total score which can range from 0 to 8. Inadequate depth of anesthesia is scored as more than three [13]. In our study, the scores were similar in both groups after intubation. We used BIS to monitored the depth of anesthesia and all intubation were performed at below 40. So, we didn't observe hypertension or tachycardia response due to laryngoscopy.

The exact mechanism of granisetron preventing hypotension after induction in adult patients is unknown and can't be explained by BJZ reflex since 5HT3 receptors are located intracardiac.[14] In the animal model, 5HT administration was caused by vasodilation and shivering and no side effects were observed in hemodynamic variables.[15] We observed that the granisetron group was more stable and closer to baseline hemodynamic variables than the control group without statistically significant variables. But in 15th minute after granisetron administration, it prevented hypotension in group G after reverse Trendelenburg position with CO_2 insufflation in 15th minute of granisetron administration.

James et al.[16] performed granisetron before the tilt test and they found that it reduced the early sympathetic component of the syncope with less decrease in systolic artery pressure. Laparoscopic cholecystectomy is a common procedure in general surgery. In this process, intraabdominal pressure increases due to CO_2 insufflation. As a result, increased intraabdominal pressure increases the vena cava pressure and causes a decrease in preload similar to that of spinal anesthesia and bleeding. And the reverse Trendelenburg position contributed to this decreased. In our study, we prevented hypotension at 15th minute of granisetron administration in reverse Trendelenburg position with CO_2 insufflation. Although we can not reveal its mechanism precisely, we think that the decrease in preload after vena cava pressure with increased intraabdominal pressure increase is since we have eliminated the effect of the heart reflex due to vagal stimulation because we have blocked intracardiac 5HT3 receptors.

Different regimens and type of 5-HT3 receptor antagonists have been used previously. Varying pharmacologic properties of different 5-HT3 receptor antagonists impede comparison. Granisetron has a plasma half-life of approximately 4.2–6.1 hours, which increases among elderly patients (>65 years); 12% of this drug is excreted unchanged via urine, with the remainder metabolized by the liver.[17] The previous study showed cardiovascular side effects after administrating 40 microgram/kg to 10 microgram/kg granisetron.[18] So, FDA advice to administered granisetron 3 mg/day total (3x1 mg). In this study, we limited by the dosage of granisetron to 1 mg like previous study about during spinal anesthesia in cesarean delivery [19]. Consequently, dosages and the type of used 5-HT3 receptor antagonists should be investigated in further studies.

There are some limitations to our study. First, we administered granisetron 5 min. before anesthesia induction. There is no study for the best time interval for granisetron administration for prevention of post-induction hypotension. Because of this many studies needs for granisetron application timing. The other, we used only the dosage of FDA suggested and we couldn't compare the effects of different dosage on hemodynamic response.

In conclusion, Granisetron prevented hypotension after reverse Trendelenburg position and CO_2 insufflation in 15th minute of granisetron administration. It can be used safely in adult patients and patients having risks of hypotension due to positions during general anesthesia.

Statement of ethics

Ethics committee approval was obtained from Ankara Dışkapı Yıldırım Beyazıt E&R Hospital Ethics Committee for our study. (Institutional Ethics Committee approval and written informed consent (Ref no 28/19, 04/04/2016) were obtained, and the study was registered in clinicaltrials.gov (NCT03180229).)

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Surgical and Medical Practices: S.A, B.N. Concept: B.N., F.K.A., Design: G.B.A, G.Ü., F.K.A., S.A. Data Collection or Processing: S.A., F.K.A. Analysis or Interpretation: S.A., G.Ü., Literature Search: B.N.,S.A. Writing: S.A., G.B.A., F.K.A

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FIB-4 Trajectories and Predictors of Fibrosis Response in Type 2 Diabetes Treated with SGLT2 Inhibitors: A Propensity-Matched 12-Month Study

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Abstract

Aim: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated favorable effects on metabolic parameters, yet their impact on liver fibrosis indices such as the Fibrosis-4 (FIB-4) score remains underexplored. Understanding the comparative efficacy of empagliflozin and dapagliflozin in modulating hepatic and metabolic markers could guide therapeutic strategies in patients with type 2 diabetes mellitus (T2DM).

Methods: This study included patients with T2DM who were initiated on empagliflozin or dapagliflozin and followed for 12 months. Clinical and laboratory parameters were assessed at baseline and 12 months, including weight, HbA1c, lipid profile, ALT, AST, and FIB-4 score. Propensity score matching was employed to identify responders (≥20% reduction in FIB-4) and non-responders. Receiver operating characteristic (ROC) analysis was performed to evaluate predictive markers for FIB-4 improvement.

Results: A total of 200 patients were analyzed. Both empagliflozin and dapagliflozin groups demonstrated significant reductions in BMI, FBG, HbA1c, and FIB-4 scores ($p < 0.001$ for all). Between-group comparisons revealed no statistically significant differences in ΔBMI, ΔHbA1c, ΔAST, or ΔFIB-4. Among responders, the baseline FIB-4 score was significantly lower (1.48±0.52 vs. 1.80±0.42; $p = 0.0445$). ROC analysis identified ΔAST ≥7 U/L as the strongest predictor of FIB-4 response (AUC = 0.875, sensitivity = 83%, specificity = 83%).

Conclusions: Both SGLT2 inhibitors significantly improved metabolic and hepatic parameters in patients with T2DM. The magnitude of AST reduction emerged as a robust predictor of FIB-4 improvement, underscoring its potential role in monitoring hepatic response to treatment.

Keywords: *SGLT2 inhibitors; empagliflozin; dapagliflozin; FIB-4 score; liver fibrosis; diabetes mellitus*

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major public health challenge associated with increasing global prevalence and substantial mortality. It accounts for approximately 1.5 million deaths annually and is a well-established risk factor for cardiovascular disease (CVD), including atherosclerosis, hypertension, and heart failure.[1,2]

Metabolic dysfunction-associated steatotic liver disease (MASLD) has recently been redefined as the leading cause of chronic liver disease worldwide. The diagnosis of MASLD requires imaging or histologic evidence of hepatic steatosis in addition to at least one of the following cardiometabolic risk factors: overweight or obesity, impaired glucose regulation or T2DM, hypertension, elevated plasma triglycerides, or reduced high-density lipoprotein (HDL).[3] Among these, T2DM is both highly prevalent and pathophysiologically linked to MASLD, with hepatic steatosis observed in up to 60% of patients with diabetes.[4] Although MASLD may be asymptomatic, disease progression can lead to hepatic inflammation, fibrosis, cirrhosis, and even hepatocellular carcinoma.[5]

Liver biopsy remains the gold standard for assessing hepatic fibrosis. However, its invasiveness, associated risks, sampling variability, and cost limit its widespread use in clinical practice.[6] In this context, the Fibrosis-4 (FIB-4) score has gained prominence as a reliable, non-invasive biomarker for detecting advanced fibrosis in patients with metabolic liver disease.[5]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as key therapeutic agents in the management of T2DM due to their cardiovascular and renal protective effects. Recent evidence also suggests potential hepatoprotective properties, including reductions in serum transaminases and improvements in hepatic fat content.[7] However, data on their influence on hepatic fibrosis remains scarce and inconclusive.

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This study aimed to evaluate the impact of SGLT2 inhibitor therapy—specifically empagliflozin and dapagliflozin—on liver fibrosis risk in patients with T2DM using serial assessment of the FIB-4 score over a 12-month follow-up period.

2. Materials and Methods

2.1. Ethical Considerations

The study was approved by the Institutional Review Board of the participating center (Approval Date: August 21, 2024; Decision No: 2024-13/2) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

2.2. Study Design and Setting

This study conducted at a tertiary care center specializing in the management of diabetes and liver disease. The objective was to evaluate the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors—empagliflozin (10 mg) and dapagliflozin (10 mg)—on liver fibrosis risk and associated metabolic parameters over a 12-month period.

2.3. Study Population

Patients aged ≥18 years with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) according to the American Diabetes Association (ADA) criteria and baseline HbA1c ≥6.5% were eligible for inclusion.

Exclusion criteria included:

- Age <18 years
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- Active malignancy
- Pregnancy or lactation
- Introduction of new antidiabetic or antihyperlipidemic agents during the follow-up period
- Chronic viral hepatitis
- History of liver transplantation
- Low or normal BMI
- Hematologic disorders requiring transfusion (e.g., transfusion-dependent beta thalassemia)
- Patients who consume alcohol
- Patients who stop taking medication

2.4. Intervention and Treatment

All patients received either empagliflozin or dapagliflozin as part of their ongoing antidiabetic treatment. No modifications were made to their baseline antidiabetic, antihypertensive, or lipid-lowering regimens during the study period. Patients who required any therapeutic changes were excluded to isolate the effect of SGLT2 inhibitors.

2.5. Data Collection and Measurements

Baseline data were collected at the initiation of SGLT2 inhibitor therapy (0th month), and follow-up data were obtained at 12 months. Recorded variables included:

- Anthropometric parameters (weight, height, BMI)
- Glycemic markers (fasting blood glucose [FBG], HbA1c)
- Lipid profile (triglycerides, LDL, HDL)
- Liver enzymes (ALT, AST)
- Renal markers (creatinine, urea)
- Platelet counts

The FIB-4 score was calculated at baseline and at 12 months using the following equation:

$$\text{Fib4 score} = \frac{Age(years) \times AST(U/L)}{Plt\left(\frac{10^9}{L}\right) \times \sqrt{ALT\left(\frac{U}{L}\right)}}$$

The FIB-4 categories were defined as follows:

- Low risk: FIB-4 < 1.30
- Intermediate risk: 1.30 ≤ FIB-4 < 2.67
- High risk: FIB-4 ≥ 2.67

2.6. Outcomes

The primary outcome was the change in FIB-4 score from baseline to 12 months. Secondary outcomes included changes in anthropometric data, glycemic control (FBG, HbA1c), lipid profile, liver enzymes, and renal parameters. A favorable FIB-4 response was defined as a ≥20% reduction from baseline.

2.7. Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed, or as median (minimum–maximum) if not. Categorical variables were summarized as counts and percentages. Within-group comparisons were performed using the Wilcoxon signed-rank test, while between-group comparisons were assessed using the Mann–Whitney U test or chi-square test, as appropriate. Associations between continuous variables were evaluated using Spearman's rank correlation.

Univariate analyses were conducted initially, followed by multivariate analyses to adjust for potential confounding factors. A two-sided p-value <0.05 was considered statistically significant.

To reduce confounding by indication, 1:1 nearest-neighbor propensity score matching (PSM) without replacement was performed using the MatchIt package in R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Covariate balance between matched groups was assessed using standardized mean differences (SMD), with values <0.1 indicating acceptable balance. SMD plots were generated using the cobalt package.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory ability of ΔAST, ΔALT, ΔHbA1c, ΔTG, and ΔBMI for predicting FIB-4 response (defined as a ≥20% reduction at 12 months). The optimal cut-off points were determined using the Youden index. ROC analyses were performed in SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

Clinical and Laboratory Changes from Baseline to 12 Months in All Patients and Treatment Groups (Table 1, Figure 1)

At 12-month follow-up, patients receiving SGLT2 inhibitors exhibited significant improvements in multiple metabolic and hepatic parameters. In the overall cohort, body weight significantly decreased from 85.8±11.1 kg to 82.5±9.4 kg (p<0.001), with parallel reductions observed in both the empagliflozin group (85.2±11.5 to 81.7±9.7 kg, p<0.001) and the dapagliflozin group (86.7±10.6 to 83.5±8.9 kg, p<0.001). BMI decreased from 31.2±4.3 to 30.0±4.0 kg/m^2 in the entire cohort (p<0.001), with comparable reductions in empagliflozin (31.3±4.4 to 29.9±4.0 kg/m^2, p<0.001) and dapagliflozin (31.9±4.5 to 30.7±4.0 kg/m^2, p<0.001) subgroups.

Glycemic control improved markedly over the study period. Mean fasting blood glucose (FBG) levels decreased from 214.6±72.8 mg/dL to 162.9±36.2 mg/dL (p<0.001), and HbA1c levels declined from 9.1±1.6% to 7.8±1.0% (p<0.001). Both empagliflozin and dapagliflozin groups demonstrated statistically significant within-group improvements in FBG and HbA1c values (all p<0.001).

Lipid profile changes were modest. Triglyceride levels decreased from 173.7±57.3 to 149.9±39.9 mg/dL (p<0.001), with similar reductions observed in both treatment groups. LDL cholesterol levels improved from 125.8±28.1 to 114.5±22.3 mg/dL overall (p<0.001), with consistent changes in both subgroups. No significant changes were observed in HDL cholesterol levels (all p>0.05).

Table 1

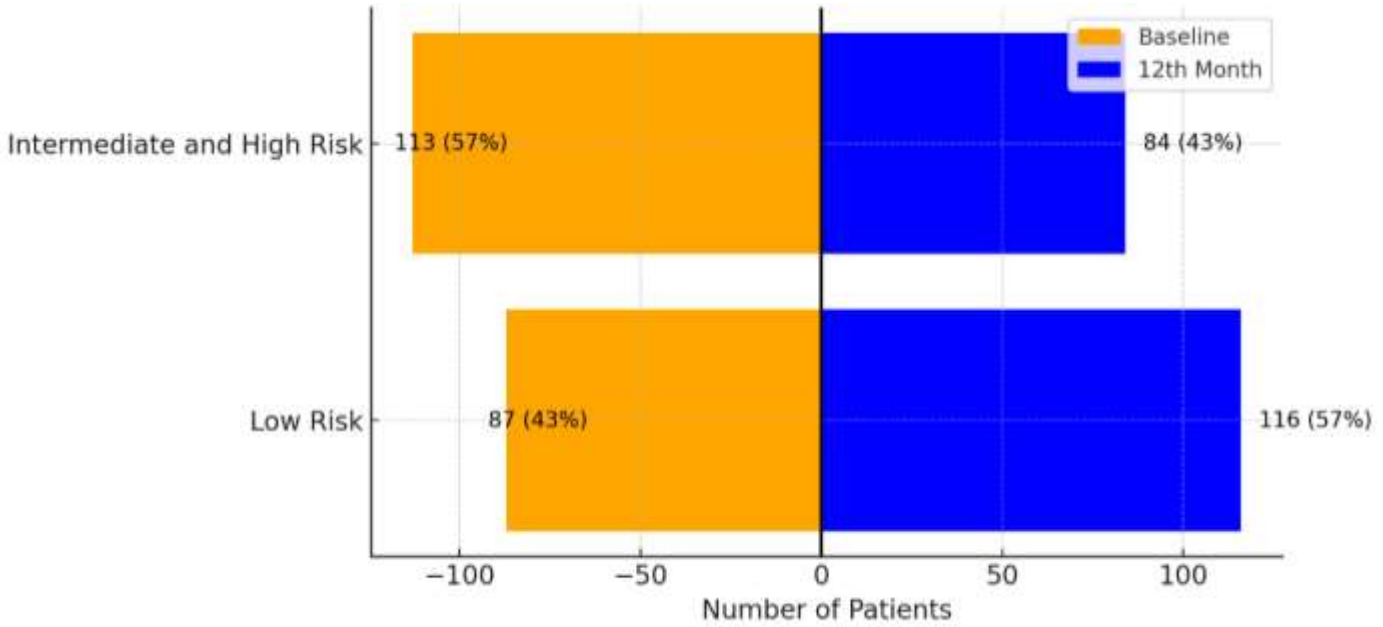
Baseline and 12-month clinical and laboratory parameters of all patients, and those treated with empagliflozin or dapagliflozin

Variable	All Patients (n=200)		Empagliflozin (n=111)		Dapagliflozin (n=89)		p1	p2	p3
	0th month	12th month	0th month	12th month	0th month	12th month			
Female, n (%)	99 (49.5%)		56 (50.5%)		43 (48.3%)		N/A	N/A	N/A
Smoker, n (%)	70 (35.0%)		36 (32.4%)		34 (38.2%)		N/A	N/A	N/A
Weight (kg)	85.8 ± 11.1	82.5 ± 9.4	85.2 ± 11.5	81.7 ± 9.7	86.7 ± 10.6	83.5 ± 8.9	<0.001	<0.001	<0.001
	85.0 (78.0–94.0)	83.0 (75.0–89.0)	83.0 (77.0–93.5)	82.0 (74.0–89.0)	86.0 (80.0–95.0)	85.0 (78.0–90.0)			
Height (cm)	166.2 ± 9.2		166.9 ± 9.7		165.3 ± 8.5		N/A	N/A	N/A
	165.0 (158.0–174.0)		165.0 (159.0–175.0)		165.0 (158.0–171.0)				
BMI (kg/m²)	31.2 ± 4.3	30.0 ± 4.0	31.3 ± 4.4	29.9 ± 4.0	31.9 ± 4.5	30.7 ± 4.0	<0.001	<0.001	<0.001
	31.2 (28.0–33.7)	29.7 (27.3–32.4)	31.2 (27.9–33.9)	29.6 (26.8–32.0)	31.2 (29.1–34.0)	30.1 (27.9–33.1)			
FBG (mg/dL)	214.6 ± 72.8	162.9 ± 36.2	213.4 ± 70.4	160.0 ± 29.3	216.1 ± 76.0	166.4 ± 43.3	<0.001	<0.001	<0.001
	192.5 (165.0–265.0)	155.0 (143.0–174.0)	190.0 (168.0–257.0)	155.0 (145.0–174.0)	201.0 (153.0–267.0)	155.0 (140.0–174.0)			
HbA1c (%)	9.1 ± 1.6	7.8 ± 1.0	9.1 ± 1.5	7.8 ± 0.9	9.0 ± 1.7	7.7 ± 1.2	<0.001	<0.001	<0.001
	9.0 (7.5–10.1)	7.7 (7.0–8.3)	9.1 (7.7–10.2)	7.8 (7.0–8.3)	8.8 (7.4–10.1)	7.5 (7.0–8.5)			
HDL (mg/dL)	43.9 ± 9.0	44.5 ± 7.9	43.3 ± 9.6	44.0 ± 8.1	44.7 ± 8.2	45.1 ± 7.6	0.1986	0.1841	0.6621
	42.0 (38.0–49.0)	42.0 (40.0–47.0)	42.0 (37.0–47.5)	42.0 (39.5–46.0)	43.0 (40.0–50.0)	43.0 (40.0–47.0)			
LDL (mg/dL)	125.8 ± 28.1	114.5 ± 22.3	125.0 ± 27.9	115.4 ± 21.8	126.9 ± 28.5	113.4 ± 23.0	<0.001	<0.001	<0.001
	128.5 (108.0–145.0)	113.5 (99.0–132.2)	129.0 (104.5–145.0)	114.0 (101.0–132.5)	128.0 (108.0–148.0)	113.0 (98.0–132.0)			
TG (mg/dL)	173.7 ± 57.3	149.9 ± 39.9	176.5 ± 59.5	150.7 ± 41.3	170.1 ± 54.5	148.9 ± 38.3	<0.001	<0.001	<0.001
	165.5 (147.0–198.2)	144.0 (132.8–161.0)	166.0 (153.0–200.5)	144.0 (129.0–161.0)	165.0 (134.0–192.0)	144.0 (137.0–161.0)			
ALT (U/L)	33.6 ± 6.9	34.8 ± 5.5	33.6 ± 7.0	34.8 ± 5.7	33.6 ± 6.8	34.7 ± 5.4	<0.001	0.0027	0.0062
	34.0 (30.0–39.0)	35.0 (33.0–39.0)	34.0 (30.0–40.0)	35.0 (33.0–39.0)	34.0 (30.0–39.0)	35.0 (33.0–38.0)			
AST (U/L)	35.1 ± 9.5	32.3 ± 6.6	34.8 ± 9.7	32.2 ± 6.7	35.5 ± 9.2	32.4 ± 6.5	<0.001	<0.001	<0.001
	35.0 (31.0–42.0)	33.0 (29.0–36.2)	34.0 (31.0–41.0)	33.0 (29.0–36.0)	35.0 (30.0–43.0)	33.0 (29.0–37.0)			
Creatinine	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	<0.001	<0.001	0.0431
(mg/dL)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.0)			
Urea (mg/dL)	34.1 ± 7.6	34.4 ± 7.8	34.8 ± 8.2	35.4 ± 8.0	33.1 ± 6.8	33.1 ± 7.5	0.5785	0.4583	0.9751
	34.0 (30.0–39.0)	34.0 (30.0–39.2)	35.0 (30.0–40.0)	35.0 (31.0–40.5)	33.0 (30.0–38.0)	33.0 (28.0–37.0)			
FIB-4 score	1.4 ± 0.5	1.2 ± 0.3	1.5 ± 0.6	1.2 ± 0.3	1.4 ± 0.5	1.2 ± 0.4	<0.001	<0.001	<0.001
	1.4 (1.1–1.7)	1.2 (1.0–1.5)	1.4 (1.1–1.7)	1.2 (1.0–1.4)	1.4 (1.0–1.8)	1.3 (1.0–1.5)			

BMI: body mass index, FBG: fasting blood glucose, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, AST: aspartate aminotransferase
Continuous variables are presented as mean ± standard deviation/median (interquartile range), and categorical variables as n (%).
p1: Within-group comparison between baseline and 12-month values in the overall cohort.
p2: Within-group comparison for patients treated with empagliflozin.
p3: Within-group comparison for patients treated with dapagliflozin.
Changes from baseline were assessed using the Wilcoxon signed-rank test for continuous variables.
Categorical variables were not analyzed longitudinally.

Figure 1

Change in FIB-4 Risk Distribution at Baseline and 12th Month



This mirrored horizontal bar chart illustrates the distribution of patients categorized as "Low Risk" and "Intermediate and High Risk" according to their FIB-4 scores at baseline and after 12 months of treatment. Orange bars represent the baseline distribution, while blue bars show the distribution at the 12th month. Labels within the bars indicate the absolute number of patients and their corresponding proportions. The chart demonstrates a net shift from higher-risk to lower-risk categories, highlighting the potential treatment-associated improvement in liver fibrosis risk stratification.

Table 2

Comparison of 12-month changes in anthropometric and laboratory parameters between treatment groups

	Dapagliflozin (n=89)		Empagliflozin (n=111)		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Δ Weight, kg	3.20 ± 2.95	3.0(-3.0-12)	3.53 ± 3.11	3.0(-2.0-13)	0.489
Δ BMI, kg/m^2	1.15 ± 1.0	0.97(-1.23-4.63)	1.24 ± 1.0	1.14(-0.63-4.66)	0.500
Δ FBG, mg/dl	49.6±53.8	46(-56-185)	53.3±60.2	40.0(-113-258)	0.816
Δ Hba1c %	1.22 ± 1.0	1.0(-0.90-3.90)	1.37 ± 0.99	1.20(-0.30-3.90)	0.211
Δ ALT (U/L)	-2.14±5.6	-2.0(-23-13)	-1.65±5.24	-1.0(-25-7)	0.514
Δ AST (U/L)	3.14±5.22	4.0(-11-18)	2.60±5.4	2.0(-11-16)	0.281
Δ Creatinine mg/dL	-0.001±0.12	0.00(-0.30-0.39)	-0.031±0.12	0.00(-0.40-0.39)	0.206
Δ FIB-4	0.26±0.56	0.21(-0.89-2.20)	0.25±0.47	0.20(-0.63-1.71)	0.993

Continuous variables are expressed as mean ± standard deviation and median (minimum–maximum). Statistical comparisons between dapagliflozin and empagliflozin groups were performed using the Mann–Whitney U test.
Δ: Change from baseline to 12 months.
Abbreviations: BMI, body mass index; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Liver enzyme levels showed favorable trends. ALT remained stable overall but demonstrated a small yet significant increase (33.6±6.9 to 34.8±5.5 U/L, p<0.001), while AST levels decreased from 35.1±9.5 to 32.3±6.6 U/L (p<0.001).

Importantly, the FIB-4 score decreased significantly from 1.4±0.5 to 1.2±0.3 in the overall population (p<0.001), with similar declines observed in the empagliflozin (1.5±0.6 to 1.2±0.3, p<0.001) and dapagliflozin (1.4±0.5 to 1.2±0.4, p<0.001) groups. These changes translated into a notable shift in FIB-4 risk categories over the 12-month period (Figure 1), with an increase in the proportion of patients categorized as low risk and a decrease in those classified as intermediate or high risk.

Serum creatinine levels increased slightly but significantly in the overall cohort (0.9±0.1 to 1.0±0.2 mg/dL, p<0.001), with a less pronounced change in the dapagliflozin group (0.9±0.1 to 0.9±0.2 mg/dL, p=0.0431). Urea levels remained stable in all groups (all p>0.05).

Comparison of 12-Month Changes Between Dapagliflozin and Empagliflozin Groups (Table 2)

Between-group analysis revealed no statistically significant differences in the magnitude of change across key clinical variables, suggesting that both empagliflozin and dapagliflozin exerted

comparable effects.

Mean weight reduction was similar between the dapagliflozin and empagliflozin groups (3.20±2.95 kg vs. 3.53±3.11 kg, p=0.489), as was BMI reduction (1.15±1.00 vs. 1.24±1.00 kg/m^2, p=0.500). HbA1c declined by 1.22±1.00% in the dapagliflozin group and by 1.37±0.99% in the empagliflozin group (p=0.211), and FBG reductions were also similar (49.6±53.8 vs. 53.3±60.2 mg/dL, p=0.816).

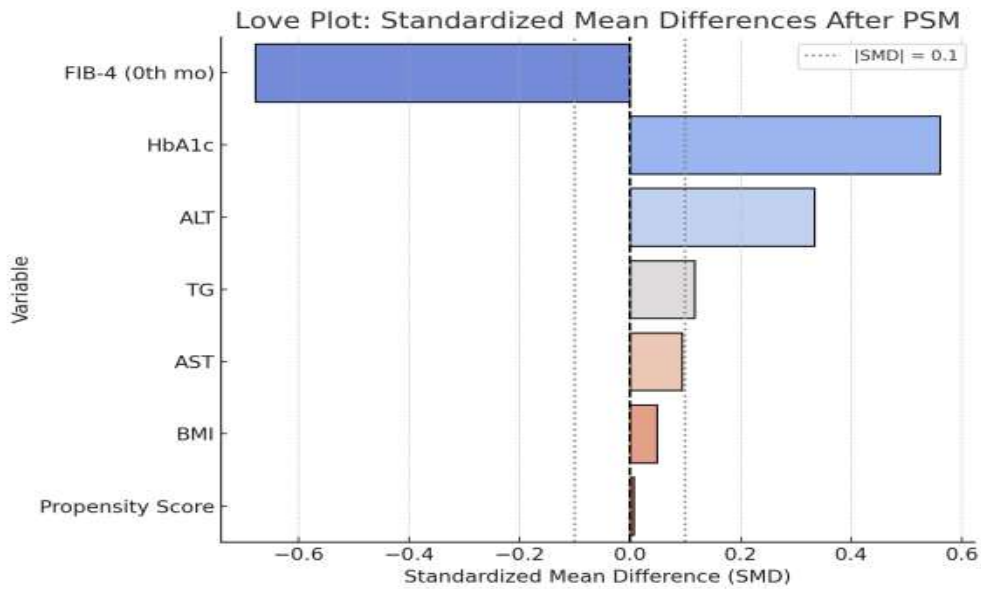
Changes in hepatic markers such as ALT (−2.14±5.6 vs. −1.65±5.24 U/L, p=0.514) and AST (3.14±5.22 vs. 2.60±5.40 U/L, p=0.281) were comparable. FIB-4 score changes did not differ significantly (0.26±0.56 vs. 0.25±0.47, p=0.993). These findings support a class effect of SGLT2 inhibitors on hepatic and metabolic outcomes.

Predictors of FIB-4 Response: Matched Analysis and ROC Evaluation (Table 3, Figure 2, Figure 3)

To assess predictors of favorable hepatic response, patients were categorized as responders (≥20% reduction in FIB-4 at 12 months) and non-responders. Propensity score matching (PSM) yielded two well-balanced groups (n=27 per group), with all baseline covariates demonstrating standardized mean differences <0.1, confirming adequate matching (Figure 2).

Figure 2

Standardized mean differences (SMDs) of baseline covariates between responder and non-responder groups following 1:1 propensity score matching.



Each bar represents the SMD for a specific covariate, comparing the matched responder and non-responder groups. The vertical dashed lines at ±0.1 denote the threshold for acceptable covariate balance. All covariates demonstrated satisfactory balance after matching (SMD < 0.1), indicating successful adjustment of baseline differences between groups.

Table 3

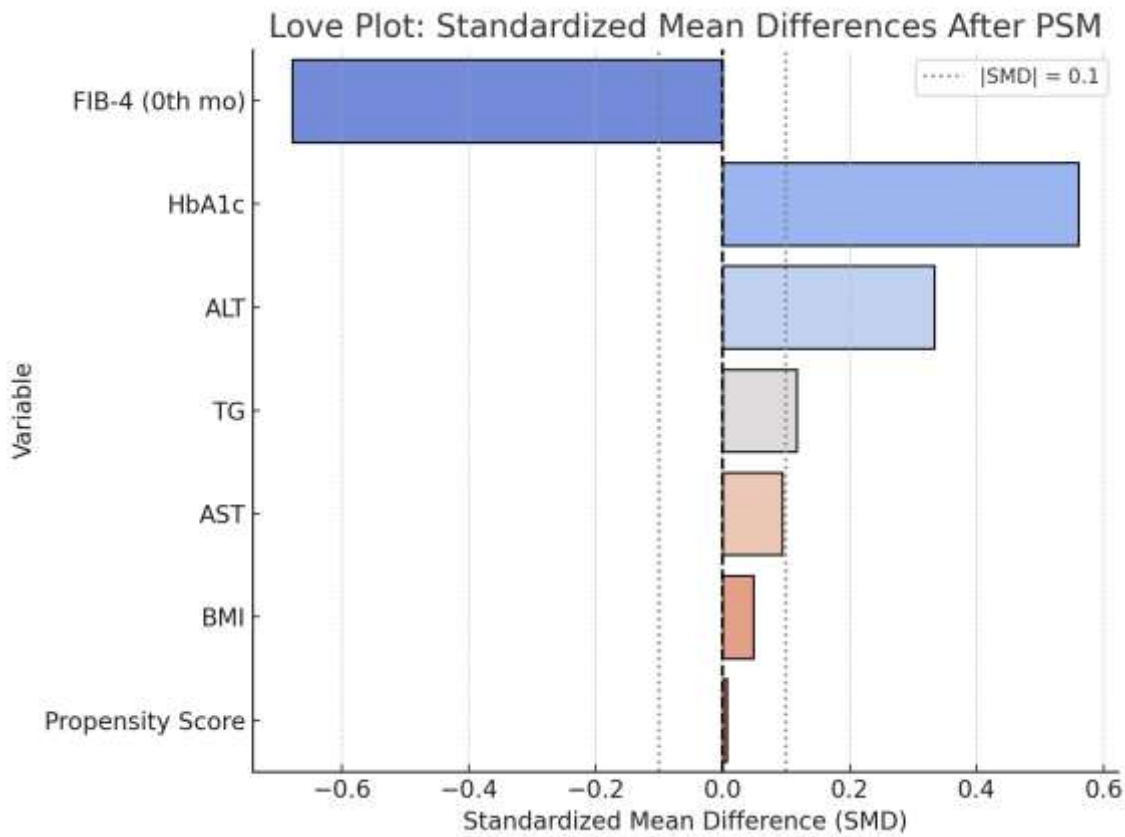
Baseline Characteristics of Propensity Score-Matched Responders and Non-Responders

	Responder (n=27)		Non-responder (n=27)		p-value
Variable	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
BMI	31.25 ± 3.82	30.72 (29.47–33.14)	31.05 ± 4.44	32.11 (27.97–33.85)	0.9369
HbA1c	9.54 ± 1.87	10.10 (7.75–11.10)	8.59 ± 1.52	8.20 (7.30–10.10)	0.1936
ALT	36.06 ± 6.14	36.00 (30.00–41.00)	33.94 ± 6.53	32.50 (30.00–40.50)	0.3723
AST	41.17 ± 5.07	41.00 (38.25–44.75)	40.56 ± 7.72	37.50 (34.25–44.00)	0.3659
TG	167.67 ± 43.01	165.00 (152.75–178.00)	163.28 ± 31.50	163.50 (155.75–176.75)	1.0
FIB-4 (baseline)	1.48 ± 0.52	1.37 (1.00–1.72)	1.80 ± 0.42	1.87 (1.50–2.08)	0.0445
Propensity Score	0.22 ± 0.13	0.19 (0.12–0.30)	0.22 ± 0.13	0.19 (0.13–0.28)	1.0

BMI: body mass index; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; FIB-4: fibrosis-4 score.Data are presented as mean ± standard deviation and median (interquartile range). Comparisons were made using the Mann–Whitney U test for continuous variables. This table summarizes the clinical and laboratory parameters after 1:1 nearest neighbor propensity score matching based on baseline covariates. All covariates showed satisfactory post-matching balance (SMD < 0.1), supporting the effectiveness of the propensity score matching procedure.

Figure 3

Standardized mean differences (SMDs) of baseline covariates between responder and non-responder groups following 1:1 propensity score matching.



Each bar represents the SMD for a specific covariate, comparing the matched responder and non-responder groups. The vertical dashed lines at ±0.1 denote the threshold for acceptable covariate balance. All covariates demonstrated satisfactory balance after matching (SMD < 0.1), indicating successful adjustment of baseline differences between groups.

Baseline characteristics were mostly similar between groups. BMI (31.25±3.82 vs. 31.05±4.44 kg/m^2, p=0.9369), HbA1c (9.54±1.87% vs. 8.59±1.52%, p=0.1936), ALT, AST, and triglycerides were all comparable (all p>0.05). However, baseline FIB-4 was significantly lower in responders (1.48±0.52 vs. 1.80±0.42, p=0.0445), suggesting a more modifiable fibrotic burden in this subgroup.

Receiver operating characteristic (ROC) analysis was performed to identify biochemical predictors of FIB-4 response (Figure 3). Among all evaluated variables, ΔAST emerged as the most accurate predictor, with an AUC of 0.875 (95% CI: 0.779–0.971), and an optimal cut-off of ≥7 U/L, yielding 83% sensitivity and 83% specificity per the Youden index. Other variables, including ΔALT, ΔHbA1c, ΔTG, and ΔBMI, showed weaker discriminative performance.

4. Discussion

In this prospective study, 12-month therapy with SGLT2 inhibitors—empagliflozin or dapagliflozin—led to significant improvements in metabolic parameters and liver fibrosis risk, as assessed by FIB-4 score, in overweight and obese patients with T2DM. Both agents resulted in reductions in BMI, fasting blood glucose, HbA1c, triglycerides, and LDL cholesterol. Importantly, FIB-4 score values declined significantly in both groups. The magnitude of AST reduction (ΔAST ≥7 U/L) emerged as a strong independent predictor of fibrosis regression, highlighting its potential as a simple clinical marker for monitoring hepatic improvement.

SGLT2 inhibitors are widely used in T2DM due to their proven cardioprotective and renoprotective properties.[1] Given the high co-prevalence of MASLD in T2DM[4] and its established association with CVD[2,3], therapeutic agents that address both metabolic and hepatic risks are of increasing clinical interest. The severity of MASLD, particularly the fibrosis stage, has been shown to be a strong predictor of adverse cardiovascular outcomes.[3]

Several recent studies have explored the hepatic benefits of SGLT2 inhibitors. A meta-analysis by Mantovani et al.[7] confirmed that SGLT2 inhibitors significantly reduce hepatic fat accumulation and transaminase levels in patients with T2DM and NAFLD. Arai et al.[8] reported a significant decrease in FIB-4 scores and improvements in transaminases, glucose, body weight, and HbA1c after 48 weeks of SGLT2 inhibitor therapy. Similarly, Shinozaki et al.[9] observed reductions in FIB-4, fasting glucose, and liver enzymes after long-term empagliflozin treatment.

In our cohort, the proportion of patients in the intermediate and high-risk FIB-4 categories decreased from 50% and 6.5% at baseline to 40.5% and 1.5%, respectively, in 12 months. These results are consistent with the findings of Liu et al., who reported post-treatment improvement in fibrosis risk categories in diabetic patients receiving SGLT2 inhibitors.[10] The E-LIFT trial

demonstrated similar effect.[11] Likewise, Kahl et al.[12] showed reductions in hepatic fat content in empagliflozin-treated patients compared to placebo, while Lai et al.[13] provided histologic evidence of steatosis, ballooning, and fibrosis improvement.

Shibuya et al.[14] found that SGLT2 inhibitors outperformed metformin in reducing hepatic steatosis and HbA1c in patients with NAFLD. Takahashi et al.[15] further demonstrated that ipragliflozin prevented new-onset NASH and improved hepatic and metabolic outcomes over time.

4.1. Mechanistic Insights

The mechanistic basis for these effects includes reductions in hepatic inflammation, oxidative stress, and stellate cell activation. Empagliflozin has been shown to downregulate fibrogenic gene expression and inflammatory cytokines in animal models[16], while dapagliflozin reduces macrophage infiltration and fibrosis signaling pathways.[17] These pleiotropic effects, combined with improvements in weight, insulin sensitivity, and lipid metabolism, are likely to contribute to the observed fibrosis regression.

4.2. Clinical Implications

These findings reinforce the potential of SGLT2 inhibitors to offer multi-organ protection in patients with T2DM, extending beyond the cardiovascular and renal systems to the liver. The identification of ΔAST as a sensitive and accessible marker for fibrosis response may facilitate non-invasive risk stratification and treatment monitoring in MASLD. Given the high prevalence of MASLD among diabetic patients, clinicians may consider SGLT2 inhibitors, particularly in individuals with suspected or early-stage fibrosis. Given the accessibility of AST in routine panels, ΔAST could serve as a simple early indicator of hepatic improvement in daily practice.

4.3. Strengths and Limitations

This study's strengths include its real-world and the direct comparison of two SGLT2 inhibitors over a 12-month period. The use of the FIB-4 score, a validated and widely accepted non-invasive fibrosis marker, enhances clinical applicability. Moreover, propensity score matching in the responder analysis strengthens the internal validity of fibrosis-related outcomes.

However, several limitations should be acknowledged. The observational design precludes definitive causal inference despite statistical adjustment. The fact that the follow-up period of the patients is 1 year is limiting in terms of predicting the effects in the longer term. Liver fibrosis was assessed using a surrogate index rather than histological confirmation or elastography. The sample size of the matched cohort was relatively small, and the study was conducted at a single tertiary care center, which may limit generalizability.

5. Conclusion

In conclusion, empagliflozin and dapagliflozin were both associated with significant improvements in hepatic and metabolic outcomes in overweight and obese patients with T2DM. The reduction in FIB-4 scores and the predictive value of AST dynamics highlight the potential antifibrotic role of SGLT2 inhibitors. These findings support the integration of liver fibrosis assessment into routine diabetes care and warrant future randomized trials incorporating histologic and imaging-based fibrosis endpoints.

Statement of ethics

The study was approved by the Institutional Review Board (Approval Date: August 21, 2024; Decision No: 2024-13/2) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Concept: NY, AE, Design: NY, AE, GZG, NK. Data Collection or Processing: NY, AE, GZG,. Analysis or Interpretation: NY, NK. Literature Search: NY, AE, GZG, NK. Writing: NY, NK.

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The Role of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the Evaluation of Renal Functions in Patients with Liver Cirrhosis

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Abstract

Aim: Early diagnosis of renal dysfunction has clinical and prognostic importance for liver cirrhosis. The disadvantages are that creatinine and blood urea nitrogen (BUN) are dependent on age and muscle mass in demonstrating renal dysfunction. There is a need for parameters that can detect renal dysfunction early in cirrhotic patients. Our aim was to investigate the sensitivity, specificity and predictive value of serum Neutrophil Gelatinase Associated Lipocalin (NGAL), serum creatinine and BUN levels against glomerular filtration rate (GFR) in the evaluation of renal function in Child A and Child B liver cirrhosis patients.

Methods: This study was conducted in a total of 84 patients with Child A or Child B liver cirrhosis who were admitted to the gastroenterology clinic between 2009 and 2010. The study was based on retrospective review of the patients' files. Clinical and laboratory parameters were recorded.

Results: We found that serum NGAL 45.8%, creatinine 88.5% and BUN 84.2% positive predictive value in defining GFR for all patients in Child A and B stages. In our study, we concluded that a NGAL value of 114.17 ng/ml and above has 68.75% sensitivity and 50% specificity in indicating glomerular filtration rate. The diagnostic utility was 47.4% and it was not found significant (p= 0.053).

Conclusions: It has been shown that serum creatinine values are more sensitive and specific than BUN and a new marker, NGAL, in terms of predicting the changes that may occur in the GFR of patients in Child A and B stages.

Keywords: *Liver cirrhosis; renal functions; NGAL*

1. Introduction

Liver cirrhosis is a chronic, diffuse and progressive liver disease characterized by loss of normal parenchymal tissue, increase in connective tissue, formation of regeneration nodules and deterioration of the vascular structure. Clinically, it is a fatal disease with hepatocellular failure and portal hypertension findings.[1] Loss or impairment of renal function is a common problem in cirrhotic patients. Renal dysfunction in cirrhotic patients worsens the prognosis, so much so that creatinine value as well as serum bilirubin and INR values are used as parameters in the MELD (Models for End Stage Liver Disease) score, which is used to predict the prognosis of patients who will undergo liver transplantation.[2]

As cirrhosis progresses to the decompensated stage, circulatory disturbance worsens, splanchnic vasodilatation becomes more pronounced and sympathetic nervous system and renin-angiotensin activity increase to maintain hemodynamic balance. Despite the increase in natriuretic substances, sodium retention, ascites and peripheral edema occur. Despite the increase in various vasoconstrictor substances in the early stages of ascites formation, renal perfusion and GFR may be normal or slightly decreased. This is due to increased renal prostaglandin production.[3] As splanchnic and systemic vasodilatation continues due to hyperdynamic circulation, systemic arterial pressure decreases and this leads to decreased renal blood flow, renal vasoconstriction develops and GFR decreases.[4] Hepatorenal syndrome (HRS) occurs in the advanced stages of cirrhosis and in the period when circulatory disturbance is the highest. In this picture, renal vasoconstriction occurs as a result of increased intrarenal vasoconstrictor substances and GFR falls below 40 ml/min/1.73m^2. The kidney is histologically normal in patients with

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hepatorenal syndrome.[5] HRS is found in 7% to 15% of patients hospitalized for cirrhosis. It is characterized by oliguria, azotemia, hyponatremia and low urinary sodium. The diagnosis of HRS can only be made after other causes of renal failure are ruled out.[6] There are 2 types of HRS. Type 1 HRS is characterized by rapid and progressive renal failure, associated with other medical complications and therapeutic interventions, an increase in serum creatinine above 2.5 mg/dl in less than 2 weeks and a decrease in creatine clearance to 20ml/min. Type 2 HRS is a slowly progressive renal impairment characterized by a stable to moderately decreased GFR with relatively well preserved liver reserve and function and has a better prognosis.[7] In one study, it was shown that 18% of 234 non-azotemic patients with cirrhosis and ascites developed functional renal failure (HRS) within 1 year and 39% within 5 years.[8] Plasma creatinine measurement is the standard biochemical test to evaluate renal function. Plasma creatinine level does not have a linear relationship with GFR. In 30% of patients with significant renal dysfunction, plasma creatinine remains within normal limits. Muscle mass accounts for 98% of the total body creatine pool. Changes in body composition due to gender, race and age, exercise and muscle diseases affect the rate of creatinine formation and alter plasma creatinine concentration and urinary creatinine excretion.[9] NGAL is a 25-kDa, 178 amino acid glycoprotein found in neutrophil granules and is an activation modulator of matrix metalloproteinase.[9] NGAL was first detected as a colorless or slightly rose-colored staining protein on E.coli bacteria.[10] NGAL belongs to the Lipocalin superfamily and is also known as Lipocalin 2. NGAL is released from renal tubular cells, hepatocytes and immune cells in various pathological conditions. As one of the effector molecules of the immune system, it has also been found to be an important modulator of cell homeostasis.[10] NGAL is the most promising biomarker for early detection of acute kidney injury and is easily excreted and detected in urine. Because it is molecularly small and resistant to degradation. NGAL accumulates in human renal cortical tubules and urine after nephrotoxic and ischemic injury. This means that NGAL is an early sensitive and non-invasive biomarker for acute renal injury.[11]

This study aims to investigate the sensitivity, specificity, and predictive value of serum Neutrophil Gelatinase-Associated Lipocalin (NGAL), serum creatinine, and BUN levels in evaluating renal function in patients with Child A and Child B stage liver cirrhosis.

2. Materials and Methods

This study was conducted in a total of 84 patients with Child A or Child B liver cirrhosis who were admitted to the gastroenterology clinic between 2009 and 2010. The study was based on a retrospective chart review. Patients with signs or symptoms of systemic infection or inflammation, elevated C-Reactive protein, suspected or confirmed malignancy, active bleeding, impaired thyroid function, comorbid pathologies such as diabetes mellitus, hypertension and coronary artery disease that may affect renal function, GFR of 40ml/minute or less, which is considered the limit for hepatorenal syndrome, and cirrhosis of the liver in Child C class were excluded. Age, gender, race and serum creatinine values were used to calculate the GFR of the patients by using the MDRD (Modification of Diet in Renal Disease) formula. The control group consisted of 28 patients of similar age and gender, 14 females and 14 males, with a mean age of 44.6±12.8 years, GFR ≥90 ml/min/1.73m^2, normal liver function and no comorbidities. Eighty-four patients were evaluated quantitatively for age, serum creatinine, GFR, albumin, bilirubin, INR, CRP and NGAL values and qualitatively for gender, presence of ascites and encephalopathy and distribution of patients according to Child classification. Gender, age, BUN, creatinine and NGAL levels were used in the descriptive characteristics of 28 individuals who constituted the healthy control group.

Statistical calculations were performed using SPSS 9.0 computer program. Student t test (Mann-Whitney U test when necessary), Chi-square and Kruskal-Wallis test were used for statistical analysis. P<0.05 was considered statistically significant.

3. Results

A total of 84 patients between the ages of 25 and 85 years, 32 (38.1%) females and 52 (61.9%) males, were included in the study. There were 48 patients (57.1%) in Child-A group and 36 patients (42.9%) in Child-B group. There were 52 (61.9%) patients with GFR >90ml/min and 32 (38.1%) patients with GFR 40-89 ml/min. Encephalopathy was not detected in any patient and ascites was present in 18 (21%) patients. The distribution of the patients included in the study according to gender, GFR, presence of ascites and cirrhosis stage is given below (Table-1).

Table 1

Distribution of patients according to gender. GFR. presence of ascites and Child classification

		n	%
Gender	Male	52	61.9%
	Female	32	38.1%
	Total	84	100.0%
GFR	40-89 ml/mn	32	38.1%
	>90ml/mn	52	61.9%
	Total	84	100.0%
Ascites	Yes	18	21.4%
	No	66	78.6%
	Total	84	100.0%
Child	A	48	57.1%
	B	36	42.9%
	Total	84	100.0%

GFR: Glomerular Filtration Rate; Child: Child-Pugh Classification (used for cirrhosis severity); n: Number of patients.

Age, BUN, serum creatinine, GFR, serum albumin, INR, total bilirubin, CRP and NGAL values were compared between Child A and B groups according to Child staging. The difference between the two groups in terms of serum albumin, INR, CRP and total bilirubin was found to be significant (Table-2, p<0.05). Consistent with the clinical stage, INR, CRP and total bilirubin were found to be higher in the Child B group compared to the Child A group, while serum albumin value, which is an indicator of the function of the liver and a negative acute phase reactant, was found to be significantly lower in the Child B group.

Based on glomerular filtration rate, age, serum creatinine, albumin, INR, BUN, NGAL, CRP and total bilirubin values were compared in patients with GFR of 90ml/minute/1.73m^2 and above with preserved renal function and in patients with low clearance renal failure with GFR between 41-89ml/minute/1.73m^2 (Table 3). The mean age of the group with low GFR was significantly higher than the group with normal GFR. Serum creatinine and BUN levels were

significantly higher in the group with low GFR compared to the normal group. There was no significant difference in serum NGAL levels between the group with low GFR and the group with normal GFR.

Table 2

Averages of some basic parameters according to Child classification

		Child		P
		A (n=48)	B (n=36)	
Age	Mean	60.46	60.67	0.932
	SD	10.10	12.16	
GFR (ml/dk/1.73m2)	Mean	94.94	96.08	0.837
	SD	25.24	24.95	
Alb(gr/dl)	Mean	3.96	3.20	<0.001
	SD	.41	.64	
INR	Mean	1.17	1.31	0.003
	SD	.15	.24	
BUN (mg/dl)	Median	13.50	15.00	0.273
	IQR	7.00	9.00	
Creatinine(mg/dl)	Median	.74	.77	0.668
	IQR	0.23	0.18	
NGAL (ng/ml)	Median	135.66	117.98	0.832
	IQR	58.63	80.7	
CRP	Median	.30	.75	<0.001
	IQR	0.56	0.64	
T. Bil(mg/dl)	Median	1.10	2.20	<0.001
	IQR	0.70	1.85	

GFR: Glomerular Filtration Rate; Alb: Albumin; INR: International Normalized Ratio; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; T. Bil: Total Bilirubin; NGAL: Neutrophil Gelatinase-Associated Lipocalin.

In all our patients with cirrhosis in Child A and B stages, a BUN value of 13mg/dl or less was shown to have a sensitivity of 65.5% and specificity of 85% in indicating a glomerular filtration rate of 90ml/min or more. Here, the diagnostic usefulness of BUN value was 69% and found to be significant (p<0.001). (Figure 1)

In all our patients with cirrhosis in Child A and B stages, a serum creatinine value of 0.79mg/dl

or less had a sensitivity of 88.4% and a specificity of 81% for glomerular filtration rate of 90ml/min or more. The diagnostic utility was 85.7% and was found to be significant (p<0.001). (Figure 2)

In all our patients with cirrhosis in Child A and B stages, NGAL values of 114.17 ng/ml and above had a sensitivity of 68.75% and specificity of 50% for glomerular filtration rate of 90ml/min and above. The diagnostic usefulness was 47.4%, which was not significant (p= 0.053). (Figure 3)

Figure 1

Diagnostic sensitivity of BUN value

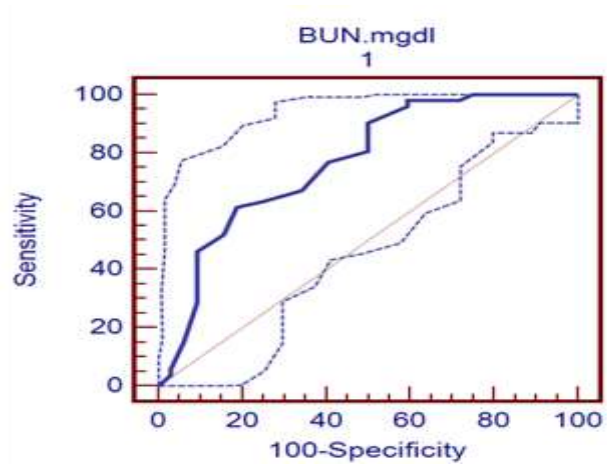

Figure 2

Diagnostic sensitivity of creatinine value

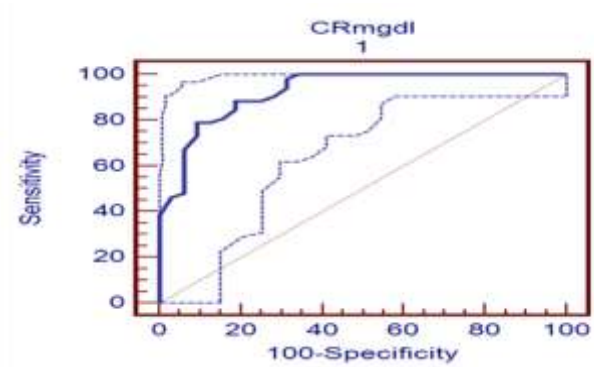

Figure 3

Diagnostic sensitivity of NGAL value

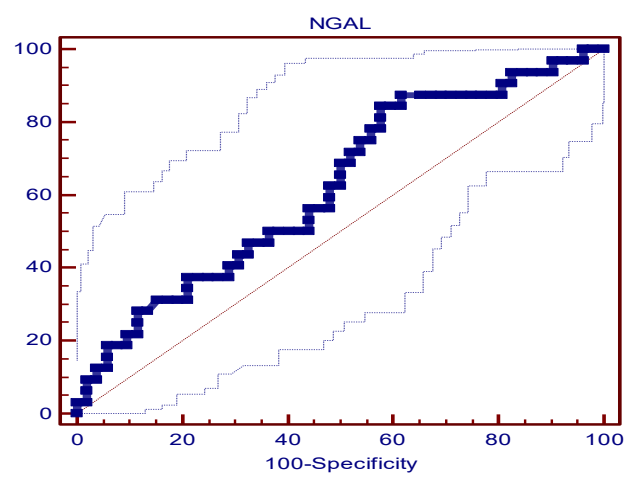

Table 3

Means, medians and distribution ranges of some basic parameters of patients classified according to GFR

		GFR		P
		40-89 ml/min (n=32)	≥90ml/min (n=52)	
Age	Mean	66.34	56.98	<0.001
	SD	7.06	11.46	
Creatinine (mg/dl)	Mean	.97	.70	<0.001
	SD	.19	.08	
Alb (gr/dl)	Mean	3.70	3.60	0.499
	SD	.71	.61	
INR	Mean	1.20	1.25	0.317
	SD	.19	.21	
BUN (mg/dl)	Median	18.00	12.00	<0.001
	IQR	8.00	6.00	
NGAL (ng/ml)	Median	140.01	115.96	0.062
	IQR	62.66	64.27	
CRP	Median	.57	.50	0.843
	IQR	0.73	0.63	
T. Bil (mg/dl)	Median	1.25	1.40	0.651
	IQR	1.65	1.25	

GFR: Glomerular Filtration Rate; Alb: Albumin; INR: International Normalized Ratio; BUN: Blood Urea Nitrogen; NGAL: Neutrophil Gelatinase-Associated Lipocalin; CRP: C-Reactive Protein; T. Bil: Total Bilirubin.

In a logistic regression analysis with renal failure as the dependent variable and age, creatinine, BUN and NGAL as independent variables, the risk of decreased glomerular filtration rate was found to be 23.9 times higher (OR 23.9, 95% CI 6.645-86.471, p<0.001) in patients with Child A and B stage liver cirrhosis above the cut-off value of 0.79mg/dl obtained for serum creatinine. (Table 4)

As a result of our study, it was determined that NGAL had a positive predictive value of 45.8%, creatinine 88.5% and BUN 84.2% for glomerular filtration rate of 90ml/min and above in patients with Child A and B stage liver cirrhosis included in the study.

4. Discussion

It is known that determination of GFR with formulas based on serum creatinine or creatinine clearance in patients with cirrhosis of the liver are not sensitive methods for optimal assessment of renal function.[12] Decreased muscle mass, anorexia, protein-restricted diet, severe hyperbilirubinemia, decreased creatinine formation in the KC, increased tubular secretion of creatinine, false low serum creatinine levels due to excessive fluid intake, and therefore false or high measurements of GFR or creatinine clearance may occur.

In our study, GFR calculated with the MDRD formula was used to evaluate renal function. This is because the MDRD formula does not include body weight. Since the MDRD formula is independent of body weight, it reflects the GFR more accurately than the GFR calculated using the Cocroft and Gault formula.[13]

Creatininee to creatinine conversion is reduced in patients with liver parenchymal disease. Decreased creatine production as a result of muscle wasting and malnutrition leads to lower basal serum creatinine levels in cirrhotic patients compared to the normal population, and as a result, normal serum creatinine levels in patients cannot exclude renal dysfunction. Muscle wasting and malnutrition were not significant in the stage of cirrhosis of the liver (Child A and B stages) of our patients included in the study and serum NGAL, creatinine and BUN were found to be positively predictive of GFR at 45.8%, 88.5% and 84.2%, respectively.

Table 4

Cut off, sensitivity, specificity, positive and negative predictive values for some of the basic parameters we evaluated in patients with liver cirrhosis in Child A and Child B stage and glomerular filtration rate of 90ml/min and above.

	Cutt Off	Sensitivity	Specificity	+PV	-PV	AUC±Se	Diagnostic Efficiency	Efficiency	P
Age , years	≤53 *	44.23	100	100	52.5	0.767±0.055	65.5	58.83	<0.001
Alb, gr/dl	≤4,3	96.15	21.87	66.7	77.8	0.538±0.064	67.9	28.94	0.559
BUN, mg/dl	≤13 *	61.54	81.25	84.2	56.5	0.770±0.055	69.1	59.29	<0.001
Cr, mg/dl	≤0,79 *	88.46	81.25	88.5	81.2	0.925±0.034	85.7	85.56	<0.001
CRP	≤1,19 *	92.31	21.87	65.8	63.6	0.513±0.065	65.5	26.32	0.843
INR	>1,12 *	78.85	43.75	69.5	56	0.555±0.064	34.5	30.80	0.391
NGAL, mg/dl	>114,17	68.75	50	45.8	72.2	0.622±0.0622	47.4	12.2	0.053
T.Bil, mg/dl	>0,7 *	86.54	25	65.2	53.3	0.529±0.064	36.9	27.98	0.649

Alb: Albumin; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; INR: International Normalized Ratio; NGAL: Neutrophil Gelatinase-Associated Lipocalin; T.Bil: Total Bilirubin; GFR: Glomerular Filtration Rate; +PV: Positive Predictive Value; -PV: Negative Predictive Value; AUC: Area Under Curve; SE: Standard Error.

In our study, a positive but low but significant correlation was found between serum NGAL and creatinine and between serum NGAL and CRP. No significant correlation was found between serum NGAL levels and age, BUN, serum albumin, bilirubin and INR which are important in prognostic staging of chronic liver disease.

Researches on the use of NGAL in acute kidney injury has focused on two areas: The use of NGAL as an early marker of acute kidney injury and its association with short-term dynamic GFR changes (use in GFR estimation). Increases in NGAL have been associated with acute kidney injury and dynamic GFR changes in models of renal ischemia during major cardiac surgery, contrast agent-induced nephropathy, renal ischemia during and after acute myocardial infarction, and renal ischemia due to septic shock 14. In our study, since serum NGAL levels were targeted not to predict acute kidney injury due to chronic liver parenchymal disease in our patients, but to predict existing low clearance renal failure and normal renal function, NGAL is not expected to provide information about dynamic GFR change.

When the studies related with the use of NGAL in chronic kidney injury were examined, immediate and prospective NGAL levels were associated with GFR measured instantaneously or prospectively (in various time periods).[15]

In our study, the positive descriptive power of NGAL was lower than creatinine. This may be due to the fact that most of our patients (n=48, 57.1%) were in Child A prognostic stage, that is, patients with compensated cirrhosis. The absence of malnutrition and muscle mass loss in patients with compensated cirrhosis may have maintained the positive predictive power of creatinine. In addition, the fact that most of the patients included in our study (n=52, 61.9%) had normal GFR (>90ml/min/1.73 m) may have weakened the correlation between NGAL, creatinine and GFR. These results show that serum creatinine is more sensitive and specific than age, BUN and a new marker, NGAL, in predicting changes in glomerular filtration rate in patients with liver cirrhosis in Child A or B stage. As a result, it has been reported that the cost of NGAL is higher compared to creatinine, there is no normal range and serum NGAL measurement is affected by many different conditions.[15] More comprehensive and large studies are needed for NGAL to be accepted as the standard method in the evaluation of renal function loss in cirrhotic patients.

5. Conclusion

In this study, it was determined that serum creatinine values are more sensitive and specific than BUN and NGAL in predicting changes in the glomerular filtration rate in patients with liver cirrhosis at Child A or B stage. NGAL, although promising, showed lower predictive power in our cohort possibly due to the predominance of patients in the compensated stage of cirrhosis. Therefore, while NGAL might be useful in early detection of acute kidney injury, its role in chronic conditions such as cirrhosis-associated renal dysfunction needs further investigation. Future large-scale and prospective studies are necessary to establish NGAL as a standard marker for renal function assessment in cirrhotic patients.

Statement of ethics

This thesis study, which was conducted using retrospective patient records, was carried out without obtaining consent, as there was no ethical approval requirement at the time of publication.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Concept: EK, MA Design: EK, MA, MP, ST, DES, Data Collection or Processing: EK Analysis or Interpretation: EK, MA, MP, Literature Search: EK, MA Writing: EK, MA

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Comparison of the Hemodynamic Response of Intravenous and Topical Lidocaine to Endotracheal Intubation

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Abstract

Aim: To compare the effects of 10% lidocaine spray and intravenous (IV) lidocaine on hemodynamic responses, postoperative throat pain, and coughing following laryngoscopy and endotracheal intubation.

Methods: A total of 120 patients, aged 18 to 65 years and scheduled for elective surgery, were randomized into two groups: Group 1 (n=60) received 10% lidocaine spray (three puffs, 30 mg), while Group 2 (n=60) was administered 1.5 mg/kg of IV lidocaine. Intubation was performed by the same individual three minutes after mask ventilation. Systolic, diastolic, and mean arterial blood pressures, along with heart rate, were recorded at baseline and at 1, 2, 4, 6, 8, and 10 minutes after intubation. Immediately upon transfer to the recovery unit, coughing and throat pain were assessed. The data were compared using ANOVA, Scheffe, and repeated measures tests, with the significance level being accepted as $p<0.05$.

Results: The comparative analysis between the groups revealed a significantly lower heart rate at 1 minute after intubation in Group 2 ($p=0.03$). No significant differences were observed in systolic and mean arterial blood pressure measurements. Diastolic blood pressure at 10 minutes was significantly lower in Group 2 ($p=0.02$). Postoperative throat pain and coughing were statistically lower in Group 1 than in Group 2 at the postoperative first hour ($p<0.001$ and $p<0.003$, respectively).

Conclusions: There was no significant difference in the suppression of hemodynamic responses between the groups, except for the heart rate measured at 1 minute. Throat pain and coughing were lower in the lidocaine spray group.

Keywords: *Intubation; hemodynamic response; throat pain; cough*

1. Introduction

Endotracheal intubation involves the placement of a tube into the trachea to secure the airway or control respiration.[1] The primary indication for endotracheal intubation is to ensure airway patency and safety in patients undergoing general anesthesia.[2] During laryngoscopy and intubation, increased plasma concentrations of norepinephrine and adrenaline lead to elevated blood pressure and heart rate, premature ventricular contractions, ventricular extrasystoles, and arrhythmias, thereby affecting myocardial oxygen consumption.[3] Following laryngoscopy and intubation, there is typically an increase in heart rate by approximately 20 beats per minute, systolic blood pressure by 50 mmHg, and diastolic blood pressure by 30 mmHg. These changes peak within 1-2 minutes and return to baseline values after 5 minutes, but they are transient and generally well-tolerated in healthy individuals without causing further problems.[1,4,5] To prevent the undesirable effects associated with intubation, several measures can be implemented, including deepening the administered general anesthesia, utilizing vasodilators that suppress the sympathoadrenal response, employing alpha and beta-adrenergic blockers, precurarization, administering short-acting opioids prior to anesthesia induction, applying topical anesthesia to the laryngeal area, and administering intravenous (IV) lidocaine a few minutes before the procedure.[1]

Lidocaine, one of the drugs utilized in the above-mentioned procedures, functions as both a local anesthetic and an antiarrhythmic agent. It exhibits analgesic effects on the dorsal horn neurons of the spinal medulla when administered intravenously. The cough reflex is suppressed by inhibiting afferent C fibers in the larynx, observed at doses above 5 mg/kg.[6] Topically applied lidocaine is rapidly absorbed through the mucosa, locally suppressing tactile stimuli. The recommended IV dose for controlling hemodynamic responses dur-

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ing airway procedures (intubation, extubation, and laryngoscopy) is 1.5 mg/kg, administered 3 minutes before the procedure.[7-10] Contraindications for lidocaine include second- and third-degree heart block, severe sinoatrial block, hypersensitivity reactions to the drug, and concurrent use of class-1 antiarrhythmic drugs. Systemic side effects primarily affect the cardiovascular and central nervous systems.[11]

To our knowledge, the effects of IV and topical lidocaine on reducing hemodynamic responses to laryngoscopy and endotracheal intubation have not been previously investigated. Thus, this study aimed to compare the efficacy of these two different administrations of lidocaine.

2. Materials and Methods

This study included 120 patients, aged 18–65 years, who were scheduled for elective surgery at the Dicle University Faculty of Medicine, had an American Society of Anesthesiology score of I-III, and no had contraindications for general anesthesia. The study received approval from the Diyarbakir Clinical Research Ethics Committee (December 21, 2009; number 2009_77) and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients, having provided informed consent, were randomized into two groups. We create randomization using computer generated random number. The exclusion criteria were a history of difficult intubation, predictors of difficult intubation (such as Thyromental distance, Interincisor gap, Mallampati class, head and neck movement), duration exceeding 30 seconds, multiple intubation attempts (more than one attempt) , hypertension, arrhythmias, beta blockers and calcium channel blockers use and previous head-neck surgeries.

Patients arrived to the operating room after 6 hours preoperative fasting and received an IV infusion of 0.9% NaCl at 10 mL/kg/hour through a 20-G cannula. No premedication was administered. Anesthesia was induced using 2 mg/kg of propofol, 2 µg/kg of fentanyl, and 0.1 mg/kg of vecuronium bromide, administered intravenously. In addition to the patients' demographic data, their baseline systolic, diastolic, and mean arterial blood pressures (SBP, DBP, and MAP, respectively), along with heart rate (HR) values, were recorded before induction. Endotracheal entubation was formed by an anesthesia assistant experienced more than three years who was blinded to the groups. Ventilation was maintained with 100% oxygen during induction. Laryngoscopy and endotracheal intubation were performed by the same individual three minutes after induction.

Group 1 (n = 60) received three puffs (30 mg) of 10% lidocaine spray 3 minutes before direct laryngoscopy. Group 2 (n = 60) received 1.5 mg/kg of 2% lidocaine IV bolus 3 minutes before laryngoscopy. Intubation was performed with 7-8-mm tubes for females and 8-9-mm tubes for males. The cuff was inflated to 20 cmH_2O to prevent air leakage. In all groups, anesthesia was maintained using 50% O_2-air (3L/min) and 2-3% sevoflurane. Hemodynamic parameters (SBP, DBP, MAP, and HR) were recorded at baseline and at 1, 2, 4, 6, 8, and 10 minutes after intubation by another anesthesia assistant who also blinded to group assignments and was not present during induction. Hypotension (SBP < 90 mmHg or >30% drop from baseline) was managed with repeated 2.5 mg doses of ephedrine. Bradycardia (HR < 50 bpm) was treated with 0.5 mg of IV atropine. Hypertension (SBP > 200 mmHg or >30% increase from baseline) was managed by increasing the inspired gas concentration by 0.5 MAC. The surgical incision was allowed following the completion of the data recording process. Postoperative throat pain and coughing were assessed upon the patient's arrival in the recovery unit.

2.1. Statistical Analysis

Given the lack of comparable studies on the effects of topical versus IV lidocaine on hemodynamic responses and postoperative throat pain, sample size calculation was based on a similar study investigating the impact of topical lidocaine on post-intubation throat pain. Using the OpenEpi program, it was determined that 60 patients per group were required to achieve 80% power and a 95% confidence interval. Simple randomization continued until target numbers were reached between January 1, 2010, and June 1, 2010.

Statistical analyses were performed using SPSS for Windows version 12.0. Student's t-test was used for analysis. The results were expressed as median or standard deviation values with the 10th and 90th percentiles. Variance analysis was utilized for age, height, and weight. The ci-square test was conducted to compare gender and the incidence of hoarseness and throat pain. The Kruskal-Wallis and Mann-Whitney tests were performed to compare symptoms between groups, with p values of <0.05 being considered significant.

3. Results

There were no significant differences between the groups in terms of age, gender, height, or weight ($p > 0.05$) (Table 1).

HR comparisons revealed a significantly lower value at 1 minute after intubation in Group 2 compared to Group 1 ($p = 0.03$). At 10 minutes, HR was significantly lower in Group 1 than in Group 2 ($p = 0.01$). No significant differences were observed at other measurement times ($p > 0.05$) (Table 2).

Table 1

Demographic data of the participants

	Group 1 (n = 60)	Group 2 (n = 60)	p
Age (years)	42.25 ± 12.10	38.98 ± 12.90	>0.05
Height (cm)	165.08 ± 6.75	165.58 ± 8.25	>0.05
Weight (kg)	70.31 ± 13.52	69.28 ± 12.72	>0.05
Gender (F/M)	33/27	35/25	>0.05

Group 1: lidocaine spray, Group 2: intravenous lidocaine, F: female, M: male, Data presented as mean ± standard deviation.

Table 2

Comparison of HR between groups

	Group 1 (n = 60)	Group 2 (n = 60)	*p*
HR, baseline	89.86 ± 15.67	83.81 ± 17.02	0.94
HR, minute 1	84.78 ± 18.00	79.31 ± 13.68	0.03*
HR, minute 2	85.35 ± 14.33	81.28 ± 15.11	0.44
HR, minute 4	81.15 ± 13.59	79.08 ± 17.06	0.54
HR, minute 6	80.80 ± 12.88	80.25 ± 14.03	0.29
HR, minute 8	80.80 ± 13.23	78.86 ± 16.77	0.32
HR, minute 10	78.51 ± 12.18	79.33 ± 18.18	0.01*

HR: heart rate, Group 1: lidocaine spray, Group 2: intravenous lidocaine, Data presented as mean ± standard deviation

SBP and MAP values did not significantly differ between the groups ($p > 0.05$). DBP was significantly lower in Group 2 at 10 minutes ($p = 0.02$), with no significant differences at other

measurement times ($p > 0.05$) (Table 3).

Any patients had hypotension and/or bradycardia treated with ephedrine or atropine prior to laryngoscopy. Upon evaluation of the incidence of side effects, it was determined that 12 patients (20%) in Group 1 and 33 patients (55%) in Group 2 experienced throat pain (Figure 1, $p < 0.001$). In addition, coughing was observed in 19 patients (31.7%) in Group 1 and 30 patients (50%) in Group 2 (Figure 2, $p < 0.003$).

Table 3

Comparison of DBP between groups

	Group 1 (n = 60)	Group 2 (n = 60)	p
DBP, baseline	79.53 ± 8.99	77.05 ± 12.05	0.01*
DBP, minute 1	68.78 ± 14.74	66.61 ± 14.50	0.55
DBP, minute 2	75.93 ± 14.24	73.05 ± 14.66	0.29
DBP, minute 4	73.81 ± 13.42	69.53 ± 15.48	0.90
DBP, minute 6	73.85 ± 12.95	70.75 ± 16.59	0.21
DBP, minute 8	74.15 ± 13.62	70.90 ± 14.47	0.78
DBP, minute 10	76.33 ± 12.41	74.45 ± 17.93	0.02*

*DBP: diastolic blood pressure, Group 1: lidocaine spray, Group 2: intravenous lidocaine, Data presented as mean ± standard deviation, *Statistically significant*

Figure 1

Incidence of sore throat

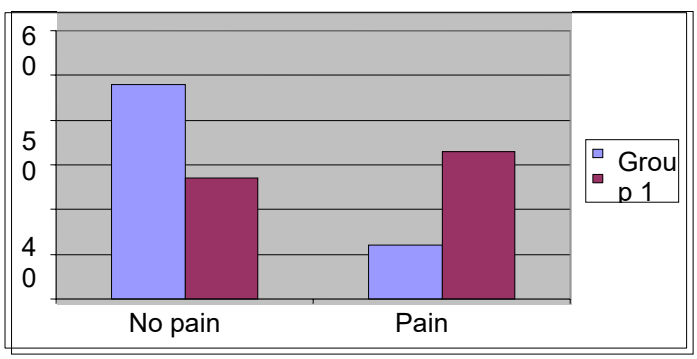
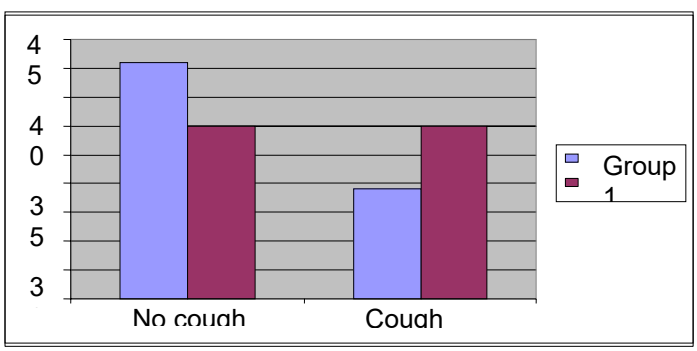


Figure 2

Incidence of cough



4. Discussion

In this study, we observed no significant difference between IV and topical lidocaine in controlling the hemodynamic responses induced by laryngoscopy and intubation, except for HR measured at 1 minute. Throat pain and coughing were found to be lower in the lidocaine spray group.

In a study comparing the efficacy of esmolol, fentanyl, lidocaine, and a placebo in preventing tachycardia and hypertension during endotracheal intubation, Helfman et al.[12] reported that only esmolol consistently and reliably prevented increases in HR and SBP associated with laryngoscopy and intubation, whereas fentanyl and lidocaine were inadequate in preventing HR increases. Consistent with our findings, the authors found that IV lidocaine was only effective in reducing HR at 1 minute following intubation, without significantly affecting SBP or MAP. In another study by van den Berg et al.[13], the effects of magnesium sulfate, esmolol, lidocaine, nitroglycerin, and a placebo on hemodynamic responses were compared. It was determined that esmolol effectively prevented increases in HR and blood pressure induced by laryngoscopy and intubation, while lidocaine and magnesium sulfate failed to suppress the hemodynamic response and were associated with an increased peak HR. Our study also revealed that while IV lidocaine resulted in a lower peak HR at 1 minute compared to the spray form, neither group had significant benefits in terms of HR and blood pressure control at other measurement times.

Sun et al.[14] investigated the hemodynamic effects of 2% topical lidocaine compared to saline during intubation and found that topical lidocaine was more effective in suppressing hemodynamic responses than saline. In contrast, our study determined that topical lidocaine was inadequate in suppressing hemodynamic responses. We consider that these discrepancies among hemodynamic studies may be attributed to variables such as the time from laryngoscopy to drug administration, the duration of laryngoscopy, the presence of premedication, and differences in the induction agents used.

Minogue et al.[15] conducted a study comparing the effects of a placebo and topical lidocaine on coughing and reported that coughing was less frequent in the group that received topical lidocaine, which is consistent with our findings. In another study, Hung et al.[16] compared the effects of benzydamine HCl spray (10 puffs, 1.5 mg), 10% lidocaine spray (10 puffs, 100 mg), and 2% lidocaine spray (10 puffs, 20 mg) applied to the endotracheal tube cuff on postoperative throat pain. They found that the benzydamine group had significantly lower incidences and severity of throat pain compared to the other groups, while the lidocaine group exhibited an increase in both the severity and frequency of throat pain, which was attributed to possible chemical mucosal damage caused by the high dosage of lidocaine. In our study, we employed much lower doses of topical lidocaine, and we did not encounter such effects. Similarly, Maruyama et al.[17] examined different doses of topical lidocaine (8%, Xylocaine pump) for preventing postoperative throat pain and hoarseness following intubation in three groups: L10 (10 puffs), L5 (five puffs), and 1 ml saline (placebo). The authors reported higher incidences of throat pain and hoarseness in the L10 group compared to the L5 and placebo groups, which was considered to be related to local mucosal irritation caused by the menthol, ethanol, and sodium saccharin components in the lidocaine spray. In our study, using a dose of 30 mg, we did not observe such effects and noted a reduction in the incidence of throat pain and coughing. This could be due to our immediate postoperative assessment of the patients, which may not have captured such complications, as well as the lower, non-irritating dose of lidocaine spray used in our study compared to the doses causing irritation in other studies. There are many factors that must be taken into consideration related to throat pain such as

head-neck surgery, positions (Trendelenburg), prolonged intubation time, high cuff pressures that could potentially affect postoperative throat pain. It is a limitation that we did not monitor cuff pressure due to technical problems, but we performed our study in low risk group (open abdominal surgeries in supine position< 120 minutes) according to throat pain. Other limitation is not to assess throat and cough during late postoperative period.

5. Conclusion

This study found that IV lidocaine was more effective than topical lidocaine in preventing the increase in HR minute only at 1 minute after intubation and laryngoscopy. Both groups were unsuccessful in suppressing hemodynamic responses. However, topical lidocaine spray was significantly effective in reducing postoperative coughing and throat pain. We think that further studies with larger sample sizes should be planned in different surgeries and patient groups.

Statement of ethics

The study received approval from the Diyarbakir Clinical Research Ethics Committee (December 21, 2009; number 2009_77).

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Author contributions

Both authors contributed equally to the article. Both authors read and approved the final manuscript.

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