2024 SEPTEMBER VOL 7 ISSUE 3

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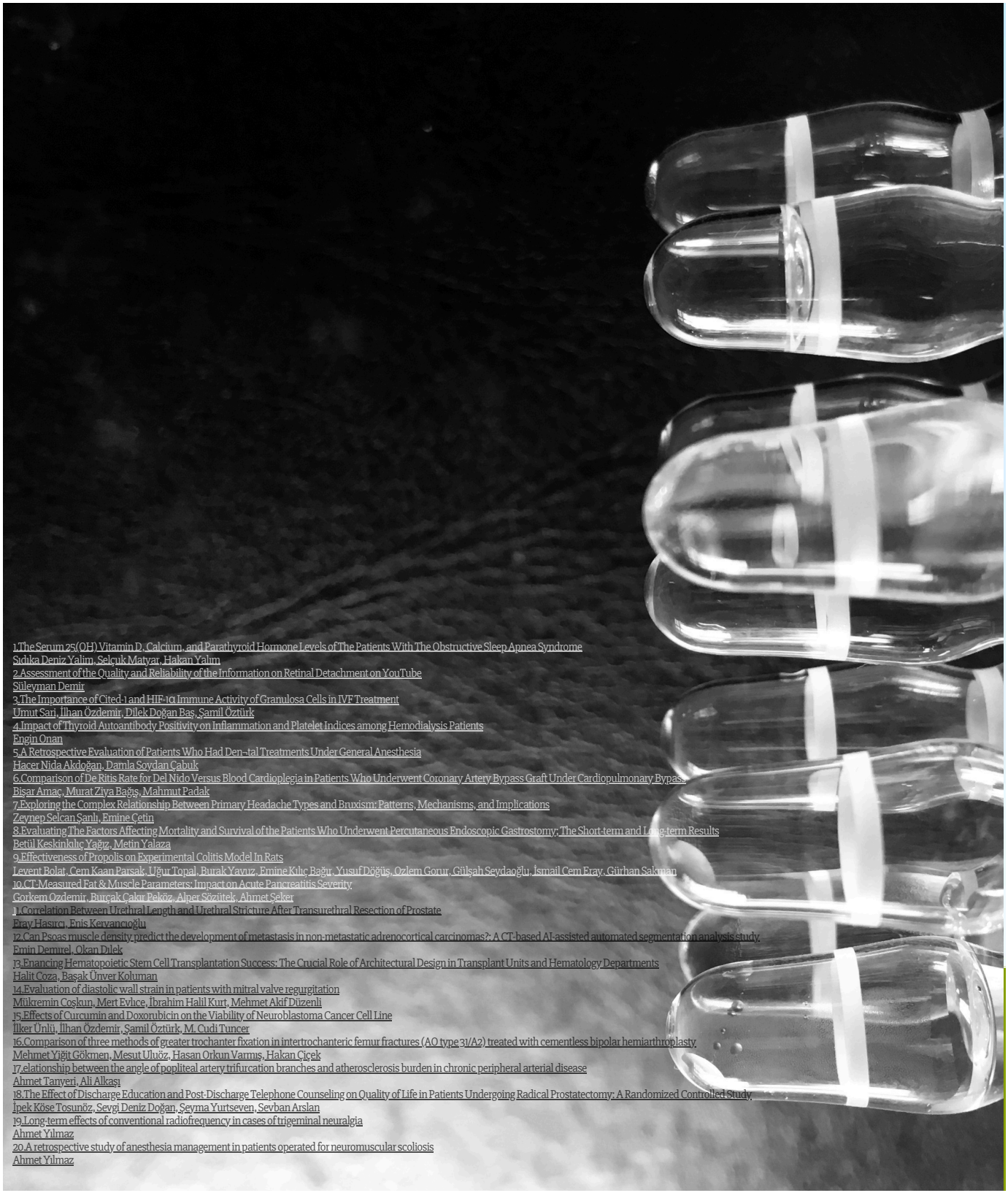

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ABSTRACTED & INDEXED

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Scilit
Türk-Medline
BASE
Google Scholar
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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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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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• If there is a direct-indirect commercial connection or financial support institution in the study, the authors; used commercial product, drug, company, etc. They should indicate to the editor on the presentation page that they have no commercial relationship with or what kind of relationship (consultant, other agreements) they have.
• 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.

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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.
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Editors should also make it clear that the reviewers must keep the manuscripts, related materials, and information they contain strictly confidential.
Reviewers and editorial staff should not publicly discuss the author's work, and reviewers should not endorse the ideas of the authors prior to publication. Reviewers should not keep the article for their personal use and should destroy the hard copies of the articles and delete the soft copies after submitting their reviews.
When an article is rejected, it is best practice for journals to delete copies from their editorial systems unless local regulations require retention.
Journals that maintain copies of rejected manuscripts should disclose this practice in the Authors' Notice.
When an article is published, journals should retain copies of the original submission, review, revision, and correspondence for at least three years, and possibly permanently, depending on local regulations, to answer future questions about the work.
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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

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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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1. On policy

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

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

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

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

- Deposits should be made as early as possible, ideally at the time of acceptance, and no later than the date of formal publication.
- When publishers will not allow OA on the funder's terms, funder policies should require grantees to seek another publisher.
- If funder policies allow embargoes before new work becomes OA, the embargoes should not exceed six months. Policies should allow no embargoes at all for uncopyrightable work.
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1.4. All university and funder OA policies should require deposit in a suitable OA repository between the date of acceptance and the date of publication. The metadata should be deposited as soon as it is available and should be OA from the moment of deposit. The full-text should be made OA as soon as the repository has permission to make it OA.

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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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2. Each table should have number and descriptive information above it.
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STATISTICS

TIME STATISTICS, ACCEPTANCE-REJECTION STATISTICS 2022

	Number of Articles Calculated	Average Time (Day)
Article Submission - Withdraw:	3	13
Article Submission - Return:	8	58
Article Submission - First Editor Assignment:	75	4
First Editor Assignment - Acceptation Decision Statistic		
Peer review:	54	58
Non peer review:	0	0
First Editor Assignment - Rejection Decision Statistic		
Peer Review:	5	84
Non-Peer Review:	7	12
Article Submission - Acceptation Decision Statistic		
Peer Review:	54	62
Non-Peer Review:	0	0
Article Submission - Rejection Decision Statistic		
Peer Review:	5	8
Non-Peer Review:	7	13

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ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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2024 SEPTEMBER VOL 7 ISSUE 3

ÇUKUROVA

ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS I

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ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS II

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The Serum 25(OH) Vitamin D, Calcium, and Parathyroid Hormone Levels of The Patients with The Obstructive Sleep Apnea Syndrome

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Abstract

Aim: Although there is evidence linking vitamin D to many neurochemical processes involved in sleep, the association between the obstructive sleep apnea and vitamin D, calcium and parathyroid hormone is still unknown, as clinical research have shown inconsistent findings. In this study we aimed to examine the hypothesis that if there is any relationship between obstructive sleep apnea and serum vitamin D, calcium and parathyroid hormone levels in order to manage treatment.

Methods: 56 patients (32 male, 24 female) admitted to the University of Health Sciences Adana City Training and Research Hospital otorhinolaryngology clinic between January 1st, 2022 and January 1st 2023 without any acute and chronic disease were included in the study. The range of participants was 18-70. In this study we examined the serum vitamin D, calcium and parathyroid hormone levels of 32 obstructive sleep apnea patients and compared their serum vitamin D, calcium and parathyroid hormone levels with the serum vitamin D, calcium and parathyroid hormone levels of 24 normal patients in the control group.

Results: When the serum vitamin D, calcium and parathyroid hormone levels of obstructive sleep apnea patients and serum vitamin D, calcium and parathyroid hormone levels of normal patients were compared we did not find a statistically significant difference which may be due to our patient density.

Conclusions: Vitamin D, calcium and parathyroid hormone levels are not likely related to the presence or absence of obstructive sleep apnea. More intervention studies are needed to better clarify the relation between the obstructive sleep apnea and vitamin D, calcium and parathyroid hormone

Keywords: *Sleep, apnea, vitamin D, calcium, parathyroid hormone*

1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is diagnosed when the Apnea-Hypopnea Index (AHI) is above 5 as determined by polysomnography, accompanied by excessive daytime sleepiness, witnessed apnea symptoms, and cardiac disorders. Recent studies have reported vitamin D deficiency in patients with OSAS. Studies independent of geography and season suggest factors other than sunlight may be influential. Additionally, vitamin D deficiency has been associated with sleep apnea, restless sleep, night sweats, and restless legs syndrome.[1] Vitamin D is a fat-soluble vitamin stored in adipose tissue. It plays a role in the skeletal system and calcium and phosphorus metabolism and balance. The term vitamin D includes cholecalciferol (D2) and ergocalciferol (D3). D2 is obtained from the diet, while D3 is synthesized in the skin via ultraviolet rays from sunlight. Hydroxylation in the liver produces 25-hydroxy (OH) vitamin D (calciferol). Further hydroxylation in the kidney results in 1,25-dihydroxy D3. The synthesis of 1,25 OH D is balanced by parathyroid hormone (PTH), serum calcium, and phosphorus levels.

Vitamin D's effects on the skeletal system are critical for bone health and development, but it also impacts the musculoskeletal system, immune system, cardiovascular system, metabolic, neurological, and psychiatric functions. Measuring vitamin D levels in the blood is done by assessing the most stable form, serum 25 OHD. It has a half-life of three weeks. Serum 25 OHD levels below 10 ng/ml are considered deficient, and levels below 20 ng/ml indicate insufficiency. Ideal levels are considered to be 30 ng/ml. With the widespread measurement of 25 OHD levels, vitamin D deficiency can be diagnosed without disease symptoms.[2]

There are varying results in the literature regarding the relationship between obstructive sleep apnea and vitamin D levels, and

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there is no consensus on the mechanisms involved. This study aims to shed light on the relationship between OSAS and levels of 25 (OH) vitamin D, calcium, and parathyroid hormone.

2. Materials and methods

The approval was obtained from the Ethics Committee of the University of Health Sciences Adana City Training and Research Hospital for this study (Ethic no: 30.05.2024/29). Written consent was obtained from the patients. Between January 1, 2018, and January 1, 2023, 56 adult patients (aged 18-65 years) who presented to the ENT outpatient clinic of University of Health Sciences Adana City Training and Research Hospital were retrospectively examined for serum 25 OH vitamin D, calcium, and parathyroid hormone levels, age, body mass index (BMI), AHI, oxygen desaturation index (ODI), mean oxygen saturation, minimum oxygen saturation, the time below 90% oxygen (TSAT90), and heart rate. Patients with chronic diseases, those using medication, those who did not agree to the tests, and those with incomplete records were excluded.

The peripheral venous blood samples were collected under standard conditions in anticoagulant-free (plain tube) vacuum biochemical tubes from fasting patients in the morning at the blood collection unit of University of Health Sciences University Adana City Training and Research Hospital. After allowing the samples to clot at room temperature for 15-20 minutes, they were centrifuged at 3000 rpm for 10 minutes. Total calcium, parathyroid hormone (PTH), and 25 (OH) vitamin D were immediately tested from the obtained serum samples. Serum 25(OH) vitamin D and PTH levels were measured using chemiluminescence with Beckman Coulter kits (CA) on a UniCel DXI 800 (Beckman Coulter Inc., CA, USA) automated immunoassay analyzer. The reference range for 25 OH Vitamin D Concentration (Vitamin D Status ng/mL) is 11.5-84.5. The reference range for PTH in individuals aged 19–67 is 12–88 pg/mL.

The serum total calcium levels were measured using Beckman Coulter kits (CA) on a Beckman UniCel DXC 5800 Synchron (Beckman Coulter Inc., CA, USA) automated analyzer via the colorimetric method. The reference range for total calcium levels in adults is 8.8 – 10.6 mg/dL.

The polysomnography tests were performed using Comet Grass (Astro-Med, Inc., West Warwick, Rhode Island, United States) devices and scored according to the American Academy of Sleep Medicine (AASM) guidelines. According to AASM 1999 criteria, an AHI below 5 is considered normal, 5-15 indicates mild OSAS, 15-30 indicates moderate OSAS, and above 30 indicates severe OSAS.

2.1. Statistical Analysis

The statistical analysis was performed using SPSS version 27.0 software (SPSS Inc., Chicago, Illinois, United States). The mean values of the study and control groups were compared using the Student t-test, and descriptive statistics were presented as mean ± standard deviation. The relationship between vitamin D and age, BMI, AHI, ODI, mean and minimum oxygen saturation, TSAT90 and heart rate was analyzed using Pearson correlation analysis. A p-value of <0.05 was considered significant.

3. Results

There were 32 obstructive sleep apnea study group (24 male, 8 female) patients and 24 normal control group (8 male, 16 female) patients.

There was no statistically significant difference in 25 (OH) vitamin D levels between OSAS patients and the control group (p=0.112). There was no significant difference in serum total calcium and parathyroid hormone levels between OSAS patients and the control group (r=0.437 and p=0.244, respectively).

A negative but not statistically significant relationship was found between 25 OHD levels and age in OSAS patients (r=-0.230, p=0.206).

A significant negative relationship was found between 25 OHD levels and BMI in OSAS patients (r=-0.379, p=0.032).

No significant relationship was found between 25 OHD levels and AHI values (r=0.186, p=0.307), ODI values (r=-0.017, p=0.927), mean oxygen saturation values (r=-0.237, p=0.192), TSAT90 levels (r=0.278, p=0.124), minimum oxygen saturation values (r=-0.296, p=1.0), or heart rate values (r=0.129, p=0.482).

No significant relationship was found between serum calcium levels and age (r=-0.214, p=0.239), BMI (r=0.056, p=0.761), AHI values (r=0.446, p=0.11), ODI values (r=0.311, p=0.083), mean oxygen saturation values (r=-0.261, p=0.149), minimum oxygen saturation values (r=-0.266, p=0.188), TSAT90 values (r=0.121, p=0.509), or heart rate (r=0.253, p=0.163) in OSAS patients.

No significant relationship was found between serum parathyroid levels and age (r=0.176, p=0.335), BMI (r=0.182, p=0.319), AHI values (r=0.42, p=0.017), ODI values (r=0.585, p=0), mean oxygen saturation values (r=-0.585, p=0.001), minimum oxygen saturation values (r=-0.169, p=0.623), TSAT90 values (r=0.403, p=0.22), or heart rate (r=0.291, p=0.106) in OSAS patients. (Table 1)

Table 1

The correlation between the parameters of the obstructive sleep apnea and the control group.

	25 OHD	Calcium	Parathyroid hormone
Age	r=-0.230 p=0.206	r=-0.214 p=0.239	r=0.176 p=0.335
Body Mass Index	r=-0.379 p=0.032	r=0.056 p=0.761	r=0.182 p=0.319
AHI	r=0.186 p=0.307	r=0.446 p=0.11	r=0.420 p=0.017
ODI	r=-0.017 p=0.927	r=0.311 p=0.083	r=0.585 p=0.000
Mean Oxygen Saturation	r=-0.237 p=0.192	r=-0.261 p=0.149	r=-0.585 p=0.001
Tsat90	r=0.278 p=0.124	r=-0.266 p=0.188	r=-0.169 p=0.623
Minimum Oxygen Saturation	r=-0.296 p=1.0	r=0.121 p=0.509	r=0.403 p=0.220
Heart Rate	r=0.129 p=0.482	r=0.253 p=0.163	r=0.291 p=0.106

4. Discussion

In our study, no relationship was found between vitamin D levels and the severity of OSA or AHI values. A negative relationship was found between vitamin D and BMI. Since vitamin D is fat-soluble, it is stored in adipose tissue, leading to lower serum vitamin D levels. This explains the negative correlation between vitamin D levels and BMI. No relationship was found between vitamin D and ODI, mean and minimum oxygen saturation levels, TSAT90, or heart rate. Vitamin D levels were not related to OSA regardless of geography and season. The study was conducted in a region with a sunny and warm climate all year round.

In the literature, Erden[3] and Bozkurt[4] et al.'s studies also found an inverse relationship between vitamin D levels and BMI. However, Erden reported that vitamin D levels were lower in OSA patients. Similar to our study, Bozkurt et al. found that vitamin D levels were not different between OSA patients and normal subjects. Salepci[5] et

al. reported no relationship between vitamin D levels and the severity of OSA or AHI values and BMI. Mete et al.[6] found no difference in vitamin D levels between OSA patients and normal subjects. Pazarlı et al.[7] also found no relationship between vitamin D and OSA.

Kerley et al.[8] reported lower 25-OHD levels in OSA patients and found that vitamin D levels were related to AHI. Vitamin D levels were inversely related to AHI, BMI, and heart rate. Piovezan et al.[9] found a relationship between low 25 OHD levels and moderate to severe OSAS and short sleep duration. Archontogeorgis et al.[10] reported that serum 25 OHD levels were low and negatively associated with AHI, ODI, TSAT90, and positively associated with mean oxygen saturation levels.

Goswami et al.[11] reported that low 25 OHD levels were associated with OSA severity and hypoxemia duration. Despite conflicting results in the literature, vitamin D and OSAS studies mostly agree that lower vitamin D levels are present in OSA patients, regardless of geography and season. Therefore, it may be beneficial to routinely measure vitamin D levels in OSA patients.

Toujani et al. found that vitamin D levels were positively associated with both mean and minimum oxygen saturation levels in patients with obstructive sleep apnea syndrome (OSAS) . While the exact mechanisms linking vitamin D to OSAS are not fully understood, several theories have been proposed, including inflammation, hypoxia, immunological responses, muscle dysfunction, and vitamin D receptor gene polymorphisms .

Neighbors et al., in their meta-analysis, reported that serum 25-hydroxyvitamin D (25 OHD) levels were significantly lower in patients with OSAS and that these levels correlated with the severity of OSAS. They also noted that the relationship between vitamin D levels and OSAS was influenced by body mass index (BMI) . Given that both untreated OSAS and vitamin D deficiency can increase cardiovascular morbidity and mortality, early diagnosis and treatment are crucial .

The limitations of our study include the small sample size of 59 patients, the lack of nationwide representation despite patients coming from various cities in the region, and the limited insight provided into the mechanisms behind the relationship between vitamin D and OSAS.

In the literature, no significant relationship was found between serum calcium levels and OSAS. However, calcium levels were within the reference range and not indicative of calcium metabolism disturbances. Our study also did not find a relationship between calcium levels and OSAS or its severity.

Parathyroid levels, though not generally reported in OSA studies, were examined in our study. No significant relationship was found between parathyroid levels and OSAS, AHI, or BMI. PTH is expected to increase in cases of vitamin D deficiency due to the role of vitamin D in calcium absorption. However, our study did not find such an association.

5. Conclusion

The relationship between vitamin D deficiency and OSAS remains inconclusive. Routine evaluation of vitamin D, calcium, and PTH levels in OSAS patients could be beneficial, but further studies are needed to clarify the underlying mechanisms and establish definitive guidelines for the management of these patients.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Health Sciences University Adana City Training and Research Hospital for this study (Ethic no: 30.05.2024/29)*

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

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

Availability of data and materials

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

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Assessment of the Quality and Reliability of the Information on Retinal Detachment on YouTube

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Abstract

Aim: This study aimed to evaluate the reliability and effectiveness of YouTube videos on retinal detachment.

Methods: A total of 85 videos were analyzed on YouTube using the search terms "retinal detachment", "retinal detachment symptom" and "retinal detachment symptoms and treatment". A total of 63 videos were included in the study. Finally, the quality and reliability of the videos included in the study were evaluated using the DISCERN score, the Global Quality Scale (GQS) and the JAMA score.

Results: The mean the DISCERN score was 55.8 ± 18.1, the JAMA score was 2.6 ± 1.4, and the GQS score was 3.7 ± 1.3 for a total of 63 videos analyzed. The total number of likes of the videos watched was 3090±1977, while the total number of dislikes was 50.2±40.6. The total duration of the videos was 392±93.1 seconds. The DISCERN, the JAMA and the GQS scores of videos uploaded by physicians were found to be statistically significantly higher than videos uploaded by YouTube health channels ($p<0.001$, $p<0.001$, $p<0.001$, respectively).

Conclusions: The quality of videos on YouTube providing information about retinal detachment is adequate. Retinal detachment is an emergency. For this reason, these videos must be adequate and not misleading, as patients first consult YouTube instead of going to the emergency room or ophthalmologist. There is therefore a need for more videos uploaded by health professionals.

Keywords: *DISCERN score, YouTube, retinal detachment, GQS score*

1. Introduction

The separation of the sensory retina from the underlying retinal pigment epithelium is known as retinal detachment rhegmatogenous retinal detachment is the most prevalent type of retinal detachment, affecting about 1 in 10,000 individuals annually.[1] Retinal detachment comes in three different forms: tractional, exudative, and rhegmatogenous.[2] Retinal detachment causes anxiety in patients and vision loss if left untreated.[3]

The Internet has become a popular source of information and 80% of Internet users turn to web-based sources for health information.[4,5] Websites like Google (www.google.com) and YouTube (www.youtube.com) are displayed at the top of these pages. Both extremely harmful and deceptive information as well as extremely helpful and educational information can be found on these platforms. The second most popular website in the world and the biggest media-sharing platform is YouTube. 5 billion videos are viewed on YouTube every day, and there are an estimated 2.3 million active users on the platform, which is a considerable increase from 30 million users in June 2018.[6,7] According to numerous studies assessing the quality of health-related YouTube videos, the majority of videos were found to be of low to medium quality, especially when posted by non-medical users.

Although there have been studies on the use of online videos on YouTube for vitreoretinal surgery training and retinal detachment surgery.[8,9] In the literature search, no recent study found that analyzed patient-oriented retinal detachment videos on YouTube that did not include surgical videos. Retinal detachment is an ocular emergency that requires urgent and rapid treatment. If left untreated and delayed, it may cause permanent vision loss. It is a very common condition with an incidence of 1 in 10,000.[1] For this reason, these videos should be sufficient and not misleading, as patients first apply to YouTube instead of going to the emergency room or ophthalmologist. This study aimed to investigate the quality and reliability of YouTube videos providing information about retinal detachment.

2. Materials and methods

2.1. Ethical disclosure

It was not necessary to obtain approval from an institutional review board for this study.

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2.2. Study design

A search was performed using the keywords " Retinal detachment", "A sign of retinal Detachment", and "Retinal detachment symptoms and treatment" searched on YouTube (http://www.youtube.com) on 30 January 2024. All video searches were performed by clearing all search history without logging into the user's account. A complete search history clearance was performed on all video searches. According to the standard search preference, videos were sorted according to the number of views. "Sort videos by relevance" was selected as the standard search preference.

This Excel file contains the following information: the video link, the quality of the uploader, the total number of views, the date the video was uploaded, the content of the video, its length (minutes), the date it was viewed, the amount of time that has passed since the video was uploaded, the number of comments, likes, and dislikes, and the Video Power Index (VPI). The video power index (VPI) is calculated using the following formula: Ratio of likes ×100/ likes+dislikes**.** Ultimately, the research design was established by expunging the computer's previous searches and cookies used for the study.

2.3. Data collection

It used the "relevance" and "view counts" filters to search for the predetermined search terms. The most popular and appropriate videos for each search term were identified, and the data from all the videos in the study was stored in an Excel file. Duplicate videos, videos that lasted less than 30 seconds, and videos unrelated to retinal detachment, in languages other than English, contained news and entertainment, or had extremely poor audio and visual quality were not included in the current investigation.

Table 1

DISCERN scoring system and GQS scale

Scores	*DISCERN Questions*
1-5	Are the aims clear?
1-5	Does it achieve its aims?
1-5	Is it relevant?
1-5	Is it clear what sources of information were used to compile the publication?
1-5	Is it clear when the information used or reported in the publication was produced?
1-5	Is it balanced and unbiased?
1-5	Does it provide details of additional sources of support and information?
1-5	Does it refer to areas of uncertainty?
1-5	Does it describe how each treatment works?
1-5	Does it describe the benefits of each treatment?
1-5	Does it describe the risks of each treatment?
1-5	Does it describe what would happen if no treatment is used?
1-5	Does it describe how the treatment choices affect overall quality of life?
1-5	Is it clear that there may be more than 1 possible treatment choice?
1-5	Does it provide support for shared decision-making?
Scores	*GQS*
1	Poor quality, not at useful for patient
2	Generally poor quality, very limited us
3	Moderate quality, somewhat useful for
4	Good quality, useful patients
5	Excellent quality, very useful for patient

GQS: Global Quality Scale

The research examined 85 videos in total. The total number of videos was excluded 22 videos. A total of 63 videos were analyzed. One investigator (expert ophthalmologist SD) examined the videos.

2.4. Evaluation of the data

The researcher used the Global Quality Scale (GQS) and Quality Criteria for Consumer Health Information (DISCERN), Journal of the American Medical Association (JAMA) score system which has been used in numerous YouTube studies in the past, to evaluate the 63 videos that were included in the study in separate settings.

The DISCERN scoring system assesses the quality of information provided to patients about treatment options and the dependability of publications[10]. Each of the 15 questions in the DISCERN scoring system is given a score between 1 and 5. This instrument assesses the medical information's objectivity and exhaustibility, particularly concerning therapy. Eight questions in the first section assess the validity of a publication (in this case, an online video), and seven questions in the second section assess the information linked to treatment[11]. The DISCERN scoring system ranges from 15 to 75 points and classifies items as very poor (15-26 points), poor(27-38 points), fair (39-50 points), good (51-62 points), and excellent (63-75 points).

A technique of scoring developed by Bernard et al. is called the Global Quality Score (GQS).[12] The ability of a video to educate patients is assessed using the Global Quality Score (GQS). A five-point Likert scale is used by the GQS system to assess the overall quality of a video's content. An outstanding quality is denoted by five points, while the lowest quality is represented by one point.

Information from health-related websites can be assessed using a well-known quality assessment tool, the Journal of the American Medical Association (JAMA) score system. There is a maximum score of four points and four possible criteria (authorship, attribution, disclosure, and currency). Each criterion is worth one point. The best quality is denoted by four points.[13, 14] The videos were categorised into 4 categories as videos uploaded by physicians, academic institutions, YouTube health channels and patients. DISCERN scoring system and GQS scoring system are shown in Table 1.[11, 12] The JAMA scoring system is shown in Table 2.[13, 14]

Table 2

JAMA Score system

JAMA Criteria (One point for each Yes, Zero points for each No)
1. Authorship: Authors and contributors, their affiliations, and relevant credentials should be provided
2. Attribution: References and sources for all content should be listed clearly, and all relevant copyright information should be noted
3. Disclosure: Website "ownership" should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest
4. Currency: Dates when content was posted and updated should be indicated

JAMA: Journal of the American Medical Association

2.5. Statistical analysis:

The Statistical Package for the Social Sciences version 25.0 program (IBM Corp., Armonk, NY) was used to statistically analyze the study's data. The values of the median (minimum-maximum) and percentages are used to express descriptive data. Using the Shapiro-Wilk test, the data's conformance to the normal distribution was examined. One-way ANOVA test was used to compare means between

groups. Tukey's test was used for post hoc comparisons. Spearman's correlation was used to evaluate the analysis of correlation. A statistically significant p-value was defined as less than 0.05.

3. Results

A total of 85 videos were analyzed. Videos unrelated to retinal detachment (n = 8), duplicate videos (n = 5), videos in any language other than English (n = 7), videos shorter than 30 seconds (n = 2) were excluded. Table 3 summarizes the descriptive statistics of the 63 included videos. The nation of origin was used to categorize 63 videos in total. In total, 52 videos originated from the USA (82.5 %); 2 videos originated from other countries (3.2 %); and the origin of 9 videos was unknown (14.2%).

Additionally, one of the following publishers (physician, academic institution, YouTube health channel, patients) and categories were given to the 63 videos. Seven of the videos belonged to physicians (n= 7, 11.1 %), 23 belonged to academic institutes (n= 23, 36.5 %), 24 belonged to YouTube health channel (n= 24, 38.0 %) and 9 belonged to patients (14.2 %).

The DISCERN, GQS, and the JAMA scores differed between 4 different video uploaders (One-way ANOVA; p< 0.001, p< 0.001, p<0.001). According to post-hoc analyses, videos uploaded by physicians are statistically significantly higher than YouTube health channels and videos uploaded by patients in terms of DISCERN score, GQS score and JAMA score (p<0.001, p<0.001, p<0.001, respectively). Similarly, videos uploaded by academic institutes were significantly higher than YouTube health channels and videos uploaded by patients in terms of DISCERN score, GQS score and JAMA score (p<0.001, p<0.001, p<0.001, respectively).

Furthermore, no significant difference was found between the DISCERN, GQS, and the JAMA scores between the videos uploaded by physicians and academic institutions in the subgroup analyses (p = 0.22, p = 0.81, p = 0.42, respectively). The DISCERN score, JAMA score and the GQS score were compared according to publishers and the results are shown in Table 4. In addition, Spearman's correlation analysis showed that there was no correlation between the DISCERN score, GQS score and the JAMA score of the videos and the year as the video year approached the present (p = 0.78, p = 0.85, p = 0.52, respectively).

Table 3

Descriptive statistics of retinal detachment videos

Descriptive statistics	Mean ± SD	Range
Number of likes	3090±1977	1-84000
Number of dislikes	50.2±40.6	0-2000
Number of total views	16.500±1.800.000	21-8.700.000
Time since upload date (day)	1639±150	30-4350
Duration (second)	392±93.1	34-3794
Number of comments	158±122	0-6615
VPI score	88.10±11.28	0-99.38
DISCERN score	55.8 ± 18.1	15–75
JAMA score	2.6 ± 1.4	0–4
GQS score	3.7 ± 1.3	1–5

JAMA: Journal of the American Medical Association; GQS: Global Quality Score. GQS: Global Quality Score; SD: Standard deviation, VPI: Video power index; JAMA: Journal of the American Medical Association;

Table 4

According to publishers DISCERN score, JAMA score, and GQS score

Publishers	n	DISCERN	JAMA	GQS
Physicians	7	66.6 ± 7.3	3.2 ± 0.8	4.2.±0.8
Academic institution	23	61.8 ± 11.8	3.7± 0.3	4.0 ± 0.6
YouTube health channel	24	52.8 ±13.4	2.4 ± 1.2	3.3 ± 0.9
Patients	9	40.8 ± 3.1	2.6 ± 1.2	2.9 ±0.3
p* values		p< 0.001	p< 0.001	p< 0.001

*JAMA: Journal of the American Medical Association; GQS: Global Quality Score, *One-way Anova Test*

4. Discussion

YouTube is the most popular video-sharing website worldwide. This platform has informative, entertaining, and practical videos. Although social media has a lot of potential to make medical information easily accessible, it is impossible to guarantee that the information is impartial and accurate. Experts are concerned about the quality of videos, particularly those that contain health-related topics. Because of this, professionals have evaluated health-related YouTube videos, and the results have generally shown that the quality of these films is poor to mediocre.[15-18] Patients may turn to YouTube in search of information because the content offered by medical professionals in patient education materials might be written at a comprehension level that is too high for them to grasp, making it impossible for them to evaluate the value, dependability, and accuracy of the information.[19]

In this study, it was determined that the DISCERN, JAMA and the GQS scores of retinal detachment videos on YouTube were good and the videos were of sufficient quality. Videos uploaded by physicians and academic institutions were found to be statistically significantly higher than YouTube health channels and videos uploaded by patients in terms of the DISCERN score, the GQS score and the JAMA score. In subgroup analyses, no significant difference was found in the DISCERN, GQS and the JAMA scores between videos uploaded by physicians and academic institutions (p = 0.22, p = 0.81, p = 0.42, respectively).

Previous studies have observed that despite the almost similar benefits of videos uploaded by physicians and non-physicians, videos uploaded by physicians have lower viewership rates, although videos uploaded by doctors are more trustworthy than those uploaded by non-physicians.[20] One possible reason for those outcomes could be that patients don't comprehend doctor-produced videos well enough. Songur et al. found that the retinal detachment surgery videos on YouTube had a medium DISCERN score, low JAMA and GQ scores, and poor-quality videos. Additionally, they found that videos with surgical content had higher scores overall than those without .[9] Although Songur et al. found retinal detachment videos to be low in terms of video quality, it is thought that the difference between the two studies may be due to the fact that they also analyzed videos containing retinal detachment surgery.

The results of this study were found to be superior in terms of video quality compared to the study of Kucuk et al. who analyzed refractive surgery videos on YouTube. Kucuk et al. showed mean GQS, DISCERN score, and JAMA score values as 1.7, 33.2 and 0.7, respectively.[21] This may be because the refractive surgery videos do not sufficiently understand the patients and the study includes videos with more patient experience than this study.

4.1. Limitations of the study

There are various restrictions on this study. The study's main drawback is that it only examined English-language videos. Additionally, keep in mind that YouTube's video specifications are subject to change. One potential limitation of this study is that it only

looked at 63 videos. Nonetheless, three search terms were employed to choose these 63 videos from 85 total videos using the "most viewed" and "relevance" filtering techniques. To the best of our knowledge, this study is the first to analyze only videos that have retinal detachment.

5. Conclusion

In conclusion, the quality of the videos on YouTube about "retinal detachment" was generally good enough. Although the quality of videos not uploaded by doctors was found to be lower, the quality of these videos was also found to be acceptable. The health professionals should share and peer-review videos that are related to health. Clear information should also be included in these expert-shared videos. It should be presented in an understandable manner rather than using technical terminology. Since retinal detachment is an urgent situation, these videos must be at a sufficient level and uploaded by physicians, since patients apply to YouTube instead of going to the emergency room or ophthalmologist.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

Authors reviewed the results and approved the final version of the manuscript.

Availability of data and materials

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

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The Importance of Cited-1 and HIF-1α Immune Activity of Granulosa Cells in IVF Treatment

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Abstract

Aim: The aim of this study was to investigate the Cited-1 and HIF-1α immune activity in granulosa cells in follicular development in patients who underwent IVF for infertility.

Methods: This study was conducted on 40 patients who were admitted to the assisted reproductive program with the complaint of infertility at the Gazi Yaşargil Training and Research Hospital Obstetrics and Gynecology Clinic IVF center between January 2022 and November 2022 and had primary or secondary infertility while starting the Ovum-Pick-Up (OPU) procedure. The fluid containing the granulosa cells was centrifuged at 3000 rpm for 10 min. The samples were fixed and processed for routine paraffine wax tissue embedding protocol. Sections were taken from paraffin blocks and immune stained with Cited-1 and HIF-1α. The preparations were examined under the microscope.

Results: HIF-1α expression was positive in membrane of granulosa cells. The nuclei were apoptotic and pyknotic. Cited1 expression was positive in membrane of granulosa cells. the cells were pyknotic

Conclusions: The high level of HIF-1α immunopositivity and negative Cited1 immunoreactivity in the immunohistochemical staining after the granulosa cells around the oocytes collected from female patients admitted to the IVF clinic and diagnosed with infertility showed that granulosa cell viability may be important on oocyte quality.

Keywords: *Granulosa cells, Oocyte, Cited-1, HIF-1α, Infertility*

1. Introduction

In vitro fertilization (IVF) is a complex series of procedures that is used in fertility. Simply, it is joining of sperm and egg in the laboratory dish. IVF is used to achieve fertility and genetic problem in people who cannot get pregnancy in normal ways. A population of somatic cells are granulosa cells that produced progesterone. During IVF procedure, granulosa cells were picked up from the patients. These cells were further analyzed for specific genes.[1] During IVF protocol, psychological and chemical stress occur and result in oxidative stress. This stress on granulosa cells also affect the oocyte and its quality. External and internal stimuli elevated oxidative stress rate, inducing apoptosis in granulosa cells.[2]

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Granulosa cells are follicular cells around the ovarian follicles. These cells close to the oocyte and their interaction support growth and maturation of oocytes. Granulosa cells surrounds the ovarian follicles and provide maturation of follicles and reacts to stimuli from adjacent cells. They secrete hormones including sex hormones estrogen and progesterone.[3] During maturation of follicles, granulosa cells also proliferated rapidly and maintains its support to developing follicles.[4] Through follicle growth, mechanism of granulosa cells proliferation rapidly is still not clear. The embryological origin of granulosa cells is still unknown.[5] Fan et al studied apoptosis rate of granulosa cells in IVF patients. They found that higher apoptosis rate in granulosa cells was a result of low ovarian reserve, with low egg and embryo numbers in IVF patients. They also stated early apoptosis can affect clinical complication in pregnancy.[6] McKenzie et al investigated a biochemical marker during embryo development to increase success rate in IVF patients. Their results showed that some genes can give clues about morphological and physiological characteristics of embryos. These can help to predict the follicular and embryonic health.[7]

HIF-1α is an important transcriptional factor that regulates cell survival in mammals when hypoxia conditions occur.[8] When HIF-1α is activated, cell metabolism is reprogrammed by the downstream expression of a number of genes. Moreover, HIF-1α can

also modulate the induction of autophagy to ensure metabolic balance.[9] Little is known about the role of HIF-1α in granulosa cells, and these cells play a very important role in healthy oocyte excretion in infertility. The CITED family are transactivators with a glutamic acid/aspartic acid-rich C-terminal domain. CITED1 plays an important role in the embryonic development process, especially in the development of the ureter, placenta and brain.[10] Abnormal embryonic development occurs in the absence of CITED1.

In this study, we investigated the Cited-1 and Hif-1α immune activity in granulosa cells in ovary during follicular development in women who applied for IVF treatment.

2. Materials and methods

This study was conducted on 40 patients who were admitted to the assisted reproductive program with the complaint of infertility at the Diyarbakır Gazi Yaşargil Training and Research Hospital Obstetrics and Gynecology Clinic IVF center between January 2022 and November 2022 and had primary or secondary infertility while starting the Ovum-Pick-Up (OPU) procedure. The patient with male factor was excluded. The fluid containing the granulosa cells was centrifuged at 3000 rpm for 10 min. Half formaldehyde and alcohol were added to the samples. The samples were centrifuged at 3000 rpm for 5 minutes and kept at +4°C overnight. The next morning, the excess liquid in the samples were poured and 1-2 drops of plasma liquid was added to the samples. The samples were placed on filter paper and 1-2 drops of eosin were dropped on it. Afterwards, the samples were taken into routine histology follow-up. Blocked tissue samples cut 3-5 microns thick with a microtome, placed on slides, and put in preparation boxes. Routine histochemical staining and immune-histochemical staining were performed on tissue samples taken from each subject and cut at 5-micron thickness. Biochemically, Prolactin, Follicle stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), anti-mullerian hormone (AMH), thyroid stimulating hormone (TSH) were detected in blood samples.

2.1. Immunohistochemical Analysis

After the granulosa cells were fixed in 10% formalin for histopathological analysis, histological follow-up procedures were performed and paraffin blocks were prepared. For immunohistochemical staining, 4-5 micron thick sections were taken from paraffin blocks. The sections taken from the slide were removed from paraffin and alcohol. Antigen retrieval was performed in a 700 W microwave for 15 minutes. After the sections were left to cool, they were washed with PBS and endogenous peroxidase blockade was performed with 3% hydrogen peroxide. It was then incubated with Ultra V blocking (catalog no. TA-015UB, ThermoFischer, USA). Primary antibodies were incubated with Cited-1 and HIF-1α (AFG Bioscientific, USA, 1/100) overnight at +4°C. Secondary antibody (TP-015-BN, ThermoFischer, USA) was then applied for 20 minutes. It was exposed to streptavidin-peroxidase (TS-015-HR, ThermoFischer, USA) for 20 minutes.

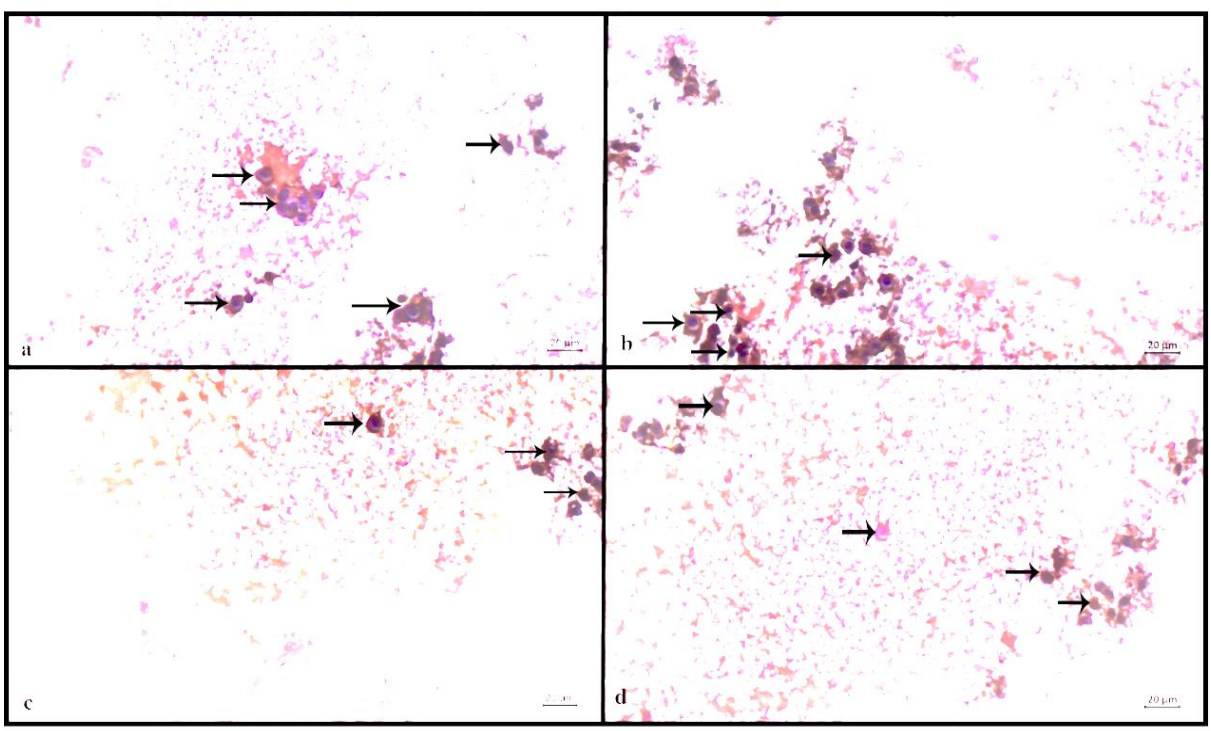
Finally, it was reacted with DAB (TA-001-HCX, ThermoFischer, US) chromogen. Hematoxylin was used for background staining11. All stained tissue samples were evaluated under Zeiss AXIO Scope 1 brand research microscope and photographed with a digital camera (Axio Cam ICc 3).

3. Results

Figure 1 shows the HIF-1α and Cited1 immune staining of granulosa cells. HIF-1α expression is expressed at the membrane level. The nuclei of the granulosa cells are peripheral, and the apoptotic process is induced. The nucleus is pyknotic. Expression was generally considered positive for HIF-1α in the membrane (Figure 1a).

Figure 1

Immune staining of granulosa cells (arrows: positive cells).



With degenerative changes, the nuclei have taken on a pyknotic appearance. This shows that hypoxia induces the apoptotic process. The hypoxia event was first seen in the membrane and then in the nucleus (Figure 1b). In particular, expression of granulosa cells was Cited-1 negative, but Cited-1 expression was positive at the membrane level. In general terms, we can say that granulosa cells are affected especially at the membrane level (Figure 1c). In the study of an aggregated population, granulosa cells were found in the periphery and the Cited-1 expression was positive. Granulosa cells were observed in the pyknotic state (Figure 1d). The average age of the patients was determined as 30.37±4.44. The average body mass index is 22.64±4.16. Additionally, when the causes of infertility are examined, it has been seen those patients with PCOS, low ovarian reserve, endometriosis and unexplained infertility apply to the clinic. Among these, unexplained infertility was the leading cause with an average of 18 patients. The demographics of the patients are shown in Table 1. Age, cause of infertility, body mass index (BMI), serum FSH, prolactin, E2, AMH levels are given.

Table 1

Demographic characteristics of the harvests included in the study.

	Overall
Number of patients, n (%)	40
Age, mean (SD)	30,37 (4,44)
BMI (kg/m2), mean (SD)	22,64 (4,16)
Infertility cause, n (%)	
• Ovulatory	12 (22.89)
• Endometriosis	6 (4.57)
• PCOS	4 (17.25)
• Unexplained	18 (51.77)
AMH (ng/ml), mean (SD)	2,84 (1.24)
TSH, (mIU / L), mean (SD)	1,82 (1,1)
E2, (Pg/mL), mean (SD)	40,9 (12.8)
FSH, (mlU/ml), mean (SD)	5,67 (3,40)
LH, (IU/L), mean (SD)	6,84 (3,75)
Prolactin, (µg/L), mean (SD)	14,6 (9,35)

4. Discussion

Oocyte and granulosa cells have direct interaction between the each other. One study showed that there are gap junctions with macula adherens between granulosa cells and oocytes by freeze-fracture electron microscopy technique.[12] Granulosa cells are associated with oocytes and always interact with each other. Through these cellular lateral junctions, granulosa cells direct the maturation and growth of follicles and oocyte inside the follicles. Metabolic precursors and nutrients are also supplied by granulosa cells to oocyte. During the maturation of oocyte, granulosa cells also secrete molecules that regulate the oocyte growth.[13] Earlier findings was considered there were a oneway communication between the oocytes and granulosa cells. However, today we know that it is bidirectional. Some factors are secreted from oocyte and these directly regulate the maturation and proliferation of granulosa cells. these factors are as oocyte-derived growth factors which are growth differentiation factor (GDF-9) and bone morphogenetic protein 15 (BMP-15)[14].

HIF-1α, a pleiotropic transcription factor, is important for the survival of mammalian cells. VEGF downstream influences the transcription of many factors such as glycolytic enzymes and glucose transporters. During the embryonic period, HIF-1α regulates vasculogenesis, tumor angiogenesis and ischemia[15]. Since cellular hypoxia develops during placenta formation, HIF-1α is activated, triggering the proliferation of trophoblasts and the formation of specific cell subtypes.[16] Tang et al. studied hypoxic cell culture model to mimic the rat follicular development model to show effect of HIF-1α. They found that hypoxia induces activation of HIF-1α and promoted rate of autophagy. By this, HIF-1α prevented the apoptosis in granulosa cells and support the follicular development.[17] Baddela et al. studied HIF-1α level in bovine granulosa cells. They stated that suppression of HIF-1α regulated the steroidogenesis. Additionally, HIF-1α affects transcription of many genes which play an important role in granulosa cells functionality.[18] In our study, granulosa cells were apoptotic and HIF-1α expression was positive. (Figure 1a-b)

Cited1, a transcriptional coactivator, likely regulates melanocyte pigmentation. It also initiates transcription, which estrogen regulates[19]. Cited1 consists of four nuclear proteins. Since there is no binding site in DNA, its role is mainly expressed as a transcriptional regulator.[20] Sriraman and his colleagues studied the progesterone receptor in granulosa cells in vitro and found that many genes that regulate the activation of the progesterone receptor in granulosa cells are controlled. It has been stated that one of these genes works depending on the progensterone receptor during ovulation and affects ovulation[21] When Hatzirodos et al. investigated the transcriptome profile of bovine granulosa cells, they found that the number of transcriptional regulators increased parallel to the growth of follicles. They found that one of the regulators was Cited1. In our study, it was observed that Cited1 expression decreased in granulosa cells with pyknotic nuclei (Figure 1 c-d).

HIF-1α is a key regulator of hypoxia-induced metabolism disruption. Many experimental studies have shown that HIF-1α ensures the survival of granulosa cells and the maintenance of follicular development in both mouse.[22] Kim et al. showed that inhibition of HIF-1α blocked hCG-dependent induced ovulation in a mouse model.[23] The findings obtained in this study also explain the cause of infertility. It showed that HIF-1a decreased in terms of immunoreactivity in granulosa cells collected from patients who came to the clinic with infertility problems. These findings showed that HIF-1α affected oocyte development as a result of hypoxia-induced cellular damage in granulosa cells and therefore played a protective role on the survival of granulosa cells.

In other experimental studies, it has been shown that FSH, another factor that facilitates the proliferation of granulosa cells and follicular development, plays a role as a critical regulator of HIF-1α activation and prevents the loss of mitochondrial balance through HIF-1α.[22,24] Another study found that oxidative stress increased after HIF-1α inhibition. They found that rat granulosa cells did not significantly increase their apoptosis when incubated under hypoxic conditions (3.0%), which are consistent with in vivo conditions. These findings indicate that granulosa cells may have a self-protective mechanism to protect themselves from hypoxia-induced apoptosis.[25] In our study results, the prominence of HIF-1a in terms of positivity suggests that CITED1 being positive may lead granulosa cells to apoptosis. Since there is no consistency in experimental studies on this subject, more comprehensive studies are needed.

5. Conclusion

As a result, it is important for individuals diagnosed with infertility to correctly diagnose the problems that prevent them from having children and to solve them with the right method. The aim of this study was to reveal one of the underlying causes of the problems encountered in the clinic and to define its relationship with infertility, if any. The findings indicate the duration of hypoxia

to which granulosa cells are exposed. In this respect, the study can be made more comprehensive and the obstacle to an important problem can be removed with more clinical data. Considering that it may be an indicator of the effect of granulosa cells on the formation of quality eggs that can be fertilized, it is thought that HIF-1a and Cited-1 may be antibodies that may be among the important markers in egg development, affecting inflammation and cell apoptosis.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Commitee for this study (07.05.2021, Decision No: 2021-760)*

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Author Contributions

Authors reviewed the results and approved the final version of the manuscript.

Availability of data and materials

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

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Impact of Thyroid Autoantibody Positivity on Inflammation and Platelet Indices among Hemodialysis Patients

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Abstract

Aim: The frequency of inflammation and autoimmune diseases is increased in hemodialysis patients. Autoimmune thyroid disease (AITD), characterized by inflammation of the thyroid gland due to immune reactivity to thyroid antigens, is common in this population. This study investigates the relationship between thyroid autoantibody positivity (TAAP), platelet function, and other inflammatory markers in hemodialysis patients.

Methods: This cross-sectional study recruited 154 hemodialysis patients, categorized into TAAP (n=22) and thyroid autoantibody negative (TAAN, n=132) groups. Patients, on thrice-weekly dialysis for at least 3 months, were not receiving levothyroxine. Data were obtained from routine monthly tests and hospital records. Exclusion criteria included active malignancy, recent chemotherapy, infections, liver cirrhosis, thalassemia, iron deficiency, hemolysis, and recent major surgery. Patients were analyzed for demographic data, metabolic parameters, platelet indices, including mean platelet volume (MPV) and platelet count (PLT), and other inflammatory markers.

Results: Patients with TAAP showed significantly higher MPV/PLT ratio (0.06/0.04, p=0.005) and lower PLT (163.05±46.67 vs 200.73±67.30, p=0.013) and platelet crit (PCT) (0.15±0.04 vs 0.18±0.06, p=0.046) compared to TAAN patients. No significant differences were observed between groups for metabolic parameters or for other inflammatory markers.

Conclusions: Our study revealed significant differences in platelet and inflammatory indices between hemodialysis patients with thyroid autoantibody positivity (TAAP) and those without (TAAN). Specifically, TAAP patients exhibited higher mean platelet volume (MPV), alongside lower platelet count (PLT) and platelet crit (PCT) levels. These findings suggest a potential association between TAAP and alterations in platelet function and activation among hemodialysis patients.

Keywords: *Hemodialysis, Autoimmune thyroid disease, Inflammatory markers,*

1. Introduction

The development of AITD occurs due to loss of immune tolerance and reactivity to thyroid autoantigens such as thyroid peroxidase (TPO), thyroglobulin (TG) and thyroid stimulating hormone receptor (TSHR). And it is known that inflammation can trigger thyroid tissue destruction by the discharge of cytokines.[1] AITD, characterized by inflammation of the thyroid gland, is prevalent among patients undergoing hemodialysis.[2] Similarly, hemodialysis patients often exhibit heightened inflammation due to various factors inherent in renal failure and dialysis treatment.[3]

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Platelets have been implicated in the pathogenesis of autoimmune disorders through interactions with immune cells and the release of pro-inflammatory factors.[4] Platelets, known for their dual role in inflammation and hemostasis, play a crucial role in modulating immune responses and maintaining vascular integrity.[5] MPV, an indicator of platelet function and activation, has emerged as a potential biomarker for assessing inflammatory states and immune dysregulation.[6] It is also known that AITD can cause changes in platelet-related indices including MPV.[7] Understanding the implications of AITD on platelet function in hemodialysis patients holds clinical relevance.[8] Identifying markers of platelet activation and inflammation could aid in risk stratification and therapeutic decision-making in this vulnerable population.[9]

This cross-sectional study aims to examine the relationship between autoantibody positivity and platelet function in hemodialysis patients. By comparing platelet and inflammatory indices between euthyroid patients with TAAP and TAAN patients, this research

seeks to elucidate potential alterations in platelet activity associated with autoantibody positivity in the hemodialysis population. Moreover, unraveling the underlying mechanisms linking autoantibody positivity and platelet dysfunction may pave the way for targeted interventions to mitigate cardiovascular complications and improve outcomes in hemodialysis patients.

2. Materials and methods

2.1. Study design and participants

This study employed a cross-sectional design to investigate the association between thyroid autoantibody positivity and platelet function in hemodialysis patients. A total of 154 hemodialysis patients were recruited for this study. Patients were categorized into two groups based on thyroid autoantibody positivity: TAAP (n=22) and TAAN patients (n=132). No patients were receiving levothyroxine treatment. Patients who had undergone hemodialysis for at least 3 months were eligible for inclusion. Patients received hemodialysis three times a week. Their laboratory results were obtained from routine monthly dialysis tests and hospital records. Exclusion criteria comprised active malignancy, history of chemotherapy, acute or chronic infection, liver cirrhosis, thalassemia, iron deficiency, hemolysis, and major surgery within the last 6 months. Patients were not receiving antithyroid therapy and had not undergone radioactive iodine or thyroid surgery. This study received approval from the Ethics Committee of Adana Şehir Training and Research Hospital in June 2024, under decision number 40, and informed consent was obtained from all participating patients.

Table 1

Demographic data of the patients.

Variables	n/ Min/Max	% / Mean±Std
Gender		
• Female	77	50
• Male	77	50
Dialysis Access		
• Av Fistula	106	68,8
• Catheter	48	31,2
Primary Disease		
• Diabetes Mellitus	40	26,0
• Hypertension	53	34,4
• Glomerulonephritis	3	1,9
• Kidney Stone	4	2,6
• Drug associated	2	1,3
• Neurogenic Bladder	2	1,3
• Polycystic Kidney Disease	2	1,3
• idiopathic	48	31,2
Age	21/92	52,62±15,35
Height (m)	1,43/2	1,64±0,09
Weight (kg)	33/130	68,87±18,15
Body Mass Index	11,69/48,93	25,36±5,80
Dialysis vintage (months)	3/252	54,09±53,49
Kt/V	1,25/2,65	1,72±0,31
URR	66/96	73,05±7,87

URR: urea reduction rate

2.2. Statistical Analysis:

Statistical analysis was performed using SPSS 18.0 software. Descriptive statistics were utilized to summarize data, presenting categorical variables as numbers and percentages, and numerical variables as mean and standard deviation. Student's t-test was employed for normally distributed numerical variables, while the Mann-Whitney U test was used for non-normally distributed variables. Chi-square and Fisher exact tests were utilized for categorical variables. Significance was set at $p<0.05$.

3. Results

In the entire cohort, 77 (50%) patients were female, while 14 out of 22 patients (63.6%) with AITD were female. The mean Kt/V was 1,720.31, and Urea reduction rate (URR) was 737.8 (Table 1). Demographic data of the patients is shown in Table 1.

Table 2

Comparison of hemodialysis patients with and without thyroid antibody positivity in terms of demographic and laboratory parameters

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Variables	Thyroid Autoantibody Positivity		p
	Yes (Mean±Std) n:22	None (Mean±Std) n: 132	
Gender (Female/Male)	14(%18,2)/8 (%10,4)	63(%81,8)/69(%89,6)	0,167
Age	60,27±15,81	51,15±15,02	0,010
Dialysis vintage	48,35±49,51	55,05±54,26	0,606*
Glucose	123	106	0,319**
Calcium-Phosphorus Index	43,53±12,79	43,51±15,10	0,995*
Parathormone	682	475	0,599**
Total Cholesterol	157,19±36,45	165,99±41,76	0,428*
Ldl Cholesterol	99,19±24,66	103,15±31,12	0,629*
Hdl Cholesterol	34,25±7,95	38,31±8,95	0,090*
Triglycerides	187	147	0,287**
Hemoglobin	10,65±1,89	11,10±1,90	0,306
Transferrin saturation (median)	0,52	0,44	0,186
Ferritin (median)	639,25	655,40	0,720
Free T3, Ref. (2,6 - 4,37 ng/L)	2,40	2,50	0,508
Free T4, Ref. (0,61-1,38ng/dL)	0,75	0,78	0,383
TSH Ref. (0,54-5,6 IU/mL)	2,22	1,76	0,085
Antithyroglobulin Antibody Ref. (0-4 IU/mL)	13	0,90	0,001
Antithyroid peroxidase Antibody Ref. (0-9 IU/mL)	15,85	0,70	0,001

*free T3: triiodothyronin, free T4: thyroxin, TSH: thyroid stimulating hormone. *The distribution was homogeneous, Student T test was used for comparison. ** The distribution was not homogeneous, Mann Whitney -U test was used for comparison in these parameters. *** Chi-square test was applied.*

There were no significant differences between patients with TAAP and TAAN patients in terms of metabolic parameters, parathormone, calcium-phosphorus product, hemoglobin, iron status (including transferrin saturation and ferritin), dialysis duration, gender, age and inflammatory parameters (Table 2). Table 2 also pre-

sents a comparison of free T3(triiodothyronin), free T4 (thyroxin), thyroid stimulating hormone (TSH), antithyroglobulin, and antithyroid peroxidase (antiTPO) levels between the two groups.

Table 3

Comparison of hemodialysis patients with and without thyroid antibody positivity in terms of inflammatory and thrombolytics parameters

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Variables	Thyroid Autoantibody Positivity		p
	Yes (Mean±Std) n:22	None (Mean±Std) n: 132	
C reactive protein	7,55	8,85	0,861**
Lymphocyte/monocytes	3,00	2,53	0,171**
Neutrophils/lymphocytes	3,01	3,36	0,517**
Neutrophils	4472,72± 1894,15	4597,73± 1730,66	0,757**
Lymphocytes	1381,82± 477,73	1424,43± 573,53	0,742**
Monocytes (median)	450	500	0,105**
PLT	163,05±46,67	200,73±67,30	0,013**
PDW (median)	17,2	17	0,327**
MPV	9,32±1,16	8,84±1,11	0,066**
PCT	0,15±0,04	0,18±0,06	0,046**
PLT/Lymphocytes	0,12	0,14	0,128**
Systemic immune inflammatory index	451,45	630,00	0,133**
MPV/PLT	0,06	0,04	0,005**
MPV/PDW	0,54	0,52	0,189**

*PLT: Platelet, PDW: Platelet derivation weal, MPV: Mean Platelet Volume, PCT: plateletcrit (MPVxPLT/1000), Systemic immune inflammatory index formula: Neutrophils X Monocytes/ Lymphocytes) ** Since the distribution was not homogeneous, Mann Whitney -U test was used for comparison of these parameters.*

4. Discussion

The findings of our cross-sectional study highlight the significant interplay between autoimmune thyroid diseases and platelet function in hemodialysis patients, underscoring the role of inflammation in modulating platelet activity and its potential implications for cardiovascular risk.

One of the notable observations from our study is the elevation in mean platelet volume MPV among euthyroid patients with TAAP compared to TAAN counterparts. These findings align with existing literature associating higher MPV levels with AITD, even in euthyroid individuals, indicative of potential platelet activation and altered hematological profiles in this context.[10] Previous research indicates that MPV tends to be elevated in patients with Hashimoto's thyroiditis, even in a euthyroid state.[11] Although MPV levels were higher in patients with autoimmune thyroiditis in our study, the difference did not reach statistical significance. However, we observed a higher MPV/PLT ratio and lower platelet counts in patients with TAAP. A meta-analysis by Cao et al. demonstrated significantly increased PLT and MPV values in patients with AITD. Interestingly, subgroup analysis revealed that elevated PLT levels were specifically associated with Hashimoto's disease and overt hypothyroidism, while MPV elevation was observed in patients with Graves' disease, hyperthyroidism, and euthyroid autoimmune thyroid disease. Conversely, patients with Hashimoto's disease and hypothyroidism exhibited lower MPV compared to healthy controls.[6]

Importantly, the elevation in MPV among hemodialysis patients with TAAP warrants attention due to its potential clinical implications, particularly in the context of cardiovascular risk. Elevated MPV levels have been linked to an increased risk of atherothrombotic complications, which is of particular concern in hemodialysis patients who already face a heightened risk of cardiovascular events.[11] In this context, elevated MPV levels may serve as a valuable indicator of increased cardiovascular risk among hemodialysis patients, reflecting its association with inflammation-related mechanisms.

Inflammatory activity in the body may influence the risk of thyroid disease, with obesity playing a significant role in this risk. Xin Yu Hu et al.'s study suggested that controlling inflammation levels could be essential for maintaining normal thyroid function.[12] In our study, the lack of significant difference in the systemic inflammatory index between the two groups highlights the potential importance of MPV as an inflammatory marker in this context.

Furthermore, our study revealed lower platelet counts and PCT levels among TAAP patients compared to TAAN patients. While the precise mechanisms underlying these differences remain to be elucidated, it is plausible that alterations in platelet production or clearance pathways may contribute to autoimmune processe.[13] The lower PCT levels observed in autoantibody-positive patients may be attributed to their lower platelet counts, highlighting the interplay between platelet indices in the context of AITD.

It is important to acknowledge the limitations of our study, including its cross-sectional design and relatively small sample size. Longitudinal studies with larger cohorts are needed to validate our findings and elucidate the temporal relationship between AITD and alterations in platelet function and hematological parameters among hemodialysis patients.

5. Conclusion

In conclusion, our study reveals a relationship between thyroid autoantibody positivity and platelet function in hemodialysis patients. Elevated MPV in TAAP patients suggests potential platelet activation, aligning with existing literature. The higher MPV/PLT ratio and lower platelet counts highlight the interplay between platelet indices and autoimmune processes. Future longitudinal studies with larger cohorts are needed to validate these findings and explore their clinical implications further.

Conflict of interest statement

The author declares that he has no financial interests related to the content of this report.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Adana City Training and Research Hospital Ethics Commitee for this study (Decision No: 2024-40)*

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Availability of data and materials

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

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A Retrospective Evaluation of Patients Who Had Dental Treatments Under General Anesthesia

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Abstract

Aim: This retrospective study aimed to evaluate the demographic and operational data of uncooperative healthy individuals and individuals with special needs who underwent dental treatments under sedation and general anesthesia.

Methods: Data of 458 patients with special needs and 77 healthy noncooperative patients who were examined at Cukurova University Faculty of Dentistry between January 2022 and May 2023 and underwent dental treatments under general anesthesia were examined retrospectively. Demographic data of the patients, American Society of Anesthesiologists (ASA) scores, mallampati (MP) scores, disability status, if they have systemic diseases, type of anesthesia (sedation/general anesthesia), anesthetic agents and analgesia used, operation duration and dental treatments, were evaluated.

Results: The average age of 535 patients who received dental treatment was 13.5±9.9 years and 58.1% (n=311) of the patients were male and 41.9% (n=224) were female. According to ASA scores, the distribution was 15.7% ASA I, 77.6% ASA II, and 6.7% ASA III. While 14.4% of the patients were systemically healthy, 16.7% had epilepsy, 12.9% had cerebral palsy, 12.1% had mental retardation, and 7.1% had Down syndrome. Of 7.1% had various comorbidities such as cardiological problems. Sedation was applied to 7.3% (n=39) of the patients, and general anesthesia was applied to 92.7% (n=496). The average anesthesia duration was 74.5±34.6 minutes. While the average restorative treatment applied to the patients was calculated as 6.45±3.9, tooth extraction 5.25±4.3, fissure sealant 2.44±2.5, pulp treatment 1.62±0.9; Trauma splint was applied to 3 patients.

Conclusions: While pre-anesthesia evaluation is very important in determining the risks in dental general anesthesia and sedation applications, the operating conditions and the general and oral health of the patients are effective in the dental treatment decision.

Keywords: *Dental treatments, general anesthesia, patient with special needs, sedation*

1. Introduction

General anesthesia is a method that requires a hospital environment, an anesthesiologist and a team, and causes depression in the motor and sensitive areas of the body, causing loss of pain sensation, muscle relaxation and loss of consciousness.[1] In pediatric dentistry, general anesthesia is frequently used as day hospitalization despite its risks in terms of optimization of treatment by both the physician and the patient.[2, 3]

In patient groups examined for pediatric dental examination and treatment, the patient's cooperation, anxiety level, treatment duration and type, dental treatment indication, patient's medical condition and many other factors are effective in determining the patient's indication for general anesthesia.

According to the American Academy of Pediatric Dentistry; People with severe fear and anxiety, mental or physical illness, situations that require urgent treatment such as many decayed teeth, dental trauma, severe abscess-cellulitis, acute pain, local anesthesia is not possible due to allergies and anatomical variations, improvement in behavior and dental compatibility. General anesthesia is indicated in patients who are expected to not recover in a short time and whose medical risks must be minimized[4].

Pre-anesthesia evaluation, anesthesia management and dental treatment plan become important in order to minimize complications and prevent the need for new general anesthesia in healthy and special needs individuals who are planned to undergo dental general anesthesia and cannot be cooperated. In this study, it was aimed to retrospectively examine the characteristics, treatments, pre-anesthesia evaluations, anesthesia practices and pain management of the patients who applied to Cukurova University Faculty of

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Dentistry, Department of Pediatric Dentistry and underwent dental treatments under sedation and general anesthesia, and to evaluate them in the light of literature knowledge.

2. Materials and methods

The present study was carried out following the ethical rules of the Declaration of Helsinki and was approved by the Cukurova University Non-Interventional Clinical Research Ethics Committee with decision no. 53 on 05.05.2023. The data of 458 special needs and 77 systemically healthy noncooperative patients who were examined at Cukurova University Faculty of Dentistry between January 2022 and May 2023 and underwent dental treatments under general anesthesia were retrospectively examined. Patient records are archived both in the classical file system and electronically, and both archives were used for the study. Demographic data of the patients, American Society of Anesthesiologists (ASA) scores, mallampati (MP) scores, disability status if they have systemic diseases, type of anesthesia (sedation/general anesthesia), anesthetic agents and analgesia used, operation duration and dental treatments were evaluated.

Dental treatment procedures include tooth extraction (permanent and primary teeth), restorative treatment (amalgam restoration, composite restoration, glass ionomer restoration and stainless steel crown), pulp therapy (root canal treatment of permanent and primary teeth, amputation of permanent and primary teeth), fissure sealant. and trauma splint.

2.1. Statistical Analysis:

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used in the statistical analysis of the data. Categorical measurements are summarized as numbers and percentages, and continuous measurements are summarized as mean and standard deviation (median and minimum-maximum where necessary).

3. Results

The average age of 535 patients who received dental treatment was 13.5±9.9 years old, and 58.1% (n=311) of the patients were male and 41.9% (n=224) were female. The distribution according to ASA scores was 15.7% ASA I, 77.6% ASA II, and 6.7% ASA III. MP score could be evaluated in 12.5% (n=67) of the patients before anesthesia, 47.8% (n=32) was MP 1, 40.3% (n=27) was MP 2, 10.4% was MP 2. (n=7) were found to be MP 3, and 1.5% (n=1) were found to be MP 4. While 14.4% of the patients were systemically healthy, 16.8% had epilepsy, 12.9% had cerebral palsy, 12.1% had mental retardation, 7.1% had down syndrome, and 7.1% had cardiological problems. Sedation was applied to 7.3% (n=39) of the patients and general anesthesia was applied to 92.7% (n=496). The average anesthesia duration was 74.5±34.6 minutes, 32.8±12.9 minutes in those subjected to sedation and 77.7±33.6 minutes in those subjected to general anesthesia. Only 1 of the patients who underwent general anesthesia had a tracheostomy, and 495 patients underwent oral intubation. It was determined that 15 (3.03%) of the patients had intubation difficulties. While the average restorative treatment applied to the patients was calculated as 6.45±3.9, tooth extraction 5.25±4.3, fissure sealant 2.44±2.5, pulp treatment 1.62±0.9; A trauma splint was applied to 3 patients. While local anesthesia was applied to 97 of the patients for analgesia, paracetamol was administered to 438 of them. Endocarditis prophylaxis was applied to 26 patients. Among anesthetic agents, the remifentanil-propofol combination was used in 257 patients who underwent general anesthesia, while sevoflurane-oxygen combination was used in 237 patients. Midazolam-ketamine combination was administered to 39 patients who were sedated. The general characteristics of the patients are in table 1, the operation-related features are in table 2, the medical status of the patients is in table 3, and the treatments applied are in table 4.

Table 1

General data of the participants

Age (Mean±SD)	13.5±9.9
Male (n(%))	311 (58.1)
Female (n(%))	224 (41.9)
ASA (n(%))	
• 1	84 (15.7)
• 2	415 (77.6)
• 3	36 (6.7)
Mallampati score(n=67) (n(%))	67 (12.5)
• 1	32 (47.8)
• 2	27 (40.3)
• 3	7 (10.4)
• 4	1 (1.5)

SD: standard deviation

Table 2

Characteristics of the operations

Operation time (min) (Mean±SD)	74.5±34.6
General Anaesthesia (min) (Mean±SD)	77.7±33.6
Sedation (min) (Mean±SD)	32.8±12.9
Anesthetic procedure (n(%))	
• General Anesthesia	496 (92.7)
• Sedation	39 (7.3)
Intubation difficulty (n=496) (n(%))	15 (3.03)
Endocarditis prophylaxis (n(%))	26 (4.9)
Anesthetic agent (n(%))	
• Remifentanil-Propofol	257(48)
• Sevofluran-Oksijen	237(44.3)
• Desflurane	2(0.4)
• Midazolam-Ketamine	39(7.3)
• Analgesia (n(%))	
• Infiltration Anesthesia	97(18.1)
• Paracetamol	438(81.9)
• Intensive Care Follow-up (n)	4

SD: standard deviation

Table 3

Medical conditions of the patients (n(%))

Epilepsy	90 (16.8)
Systemically healthy	77 (14.4)
Cerebral Palsy	69 (12.9)
Other	65 (12.1)
Mental Retardation	65 (12.1)
Autism	44 (8.2)
Down Syndrome	38 (7.1)
Cardiological disorders	38 (7.1)
Haematological disorders	19 (3.6)
Psychiatric disorders	14 (2.4)
Hydrocephalia	10 (1.9)
Immun deficiency disorders	6 (1.2)

Other: Hearing impairment, Williams syndrome, Sturge-Weber syndrome, cystic fibrosis, Gaucher disease, Kabuki make-up syndrome, Lesch-Nyhan syndrome, Fanconi Bickel syndrome, biliary atresia, Cornelia de Lange syndrome, Rotor syndrome, Ataxia telangiectasia, Prader Willi syndrome HIVEP2 gene-associated intellectual disability, medulloblastoma, mucopolysaccharidosis type 3, microcephaly, Wilms tumour, cleft palate, Turner syndrome, fibrosarcoma, Apert syndrome, Beckwith-Wiedemann syndrome, Rett syndrome, Aicardi-Goutieres syndrome, osteogenesis imperfecta, epidermolysis bullosa, muscular dystrophy, Goldenhar syndrome, dandy-walker syndrome, neurofibromatosis,

Table 4

Dental procedures

Treatments	Mean±SD
• Restorative treatment (Mean±SD)	6.45±3.9
• Tooth extraction (Mean±SD)	5.25±4.3
• Fissur sealent (Mean±SD)	2.44±2.5
• Pulp treatment (Mean±SD)	1.62±0.9
• Trauma splint (n(%))	3 (0.6)

SD: standard deviation

4. Discussion

General anesthesia and sedation are safely applied on a daily basis in the dental treatment of uncooperative healthy individuals of all age groups and individuals with special needs.[5] Gender disproportionality has been noticed in many studies, but it has not been clearly stated why men so consistently outnumber women.[6, 7] Studies conducted with individuals with special needs have shown that patients have a wide age range ranging from 1 to 50 years old.[8, 9] This study population was found to be comprised of the majority of males and a wide age range ranging from 2 to 53 years. Systemically healthy individuals were found to be between the ages of 2-12. From these data, it can be seen that men are more compliant with dental treatments.

Priority should be given to dental treatments for individuals with special needs who have high-risk medical conditions, congenital heart diseases, and immunodeficiency manifested by signs and symptoms of dental treatment needs.[10] In this retrospective study, 85.6% of the individuals who received dental treatments were individuals with special needs and 14.4% were systemically healthy individuals. Mallineni and Yiu recently published a retrospective study on dental treatment provided to individuals with special needs in Hong Kong and found that the population consisted of 60% of individuals with neurological problems, 12% with cardiovascular problems and 11% with various syndromes.[7] The main underlying problems of individuals with special needs are 16.7% epilepsy, 12.9% cerebral palsy, 12.1% mental retardation, 7.1% Down syndrome, 7.1% cardiological problems. constitutes. In this study, 84.3% of the patients who received dental treatments were evaluated as ASA 2, 3, while 15.7% were evaluated as ASA 1.

An MP score of 3 or 4 should suggest that there may be difficulty in intubating the patient.[5] With a good pre-anesthesia examination, difficulties that the patient may experience during intubation can be predicted. However, intubation difficulties cannot be detected due to the lack of cooperation with individuals requiring special care during the examination.[11] In this study, the MP score could be evaluated in 67 patients, and the number of patients with an MP score of 3 or 4 was eight. However, the number of patients with intubation difficulties is fifteen. In individuals with special needs, there may be reasons such as some syndrome-related chronofacial anomalies, obesity, scoliosis, the size of the anatomical structures in the neck area and the frequent occurrence of respiratory diseases.[12]

Depending on the patient and the operation, sedation or general anesthesia is preferred. Indications for dental general anesthesia include patients with craniofacial anomalies who need dental treatment, orofacial trauma or jaw fractures, patients who are too young to cooperate or have special needs, patients with serious systemic diseases (epilepsy, haematological diseases, cardiological diseases, allergies, etc.), patients and patients whose dental treatments are planned to be performed in a single session.[4, 13, 14] In this study, all dental treatments of individuals with special needs and uncooperative healthy young children were performed in a single session. The average operation time was 74.5±34.6 minutes, 77.7±33.6 minutes in patients under general anesthesia and 32.8±12.9 minutes in patients under sedation. It was observed that 92.7% of the patients were administered general anesthesia. The long operation time, depending on the number of teeth to be treated, was a major factor in deciding on general anesthesia.

For patients with cardiological problems, necessary precautions should be taken to prevent the risk of infective endocarditis that may occur during dental treatments. However, the high probability of cardiological problems in patients with Down syndrome should not be overlooked in the pre-anesthesia evaluation of patients[15]. In this study, cardiology consultation was requested for every patient with cardiological problems and Down syndrome, and in line with the recommendations of cardiologists, antibiotic prophylaxis for infective endocarditis was administered to 26 patients, and no complications developed.

Dental treatments performed using general anesthesia and sedation are planned on a daily basis. Since there is a strong relationship between discharge and operation time, the operation time is limited to 90 minutes in outpatient treatments[16]. In this study, the average operation time was 74.5±34.6 minutes and all but 4 patients were treated on a daily basis. Four patients who were followed up in postoperative intensive care had muscular dystrophy. In these patients, sensitivity to sedatives, anesthetics and muscle relaxants, respiratory and cardiovascular complications may occur during and after the operation, and recovery after anesthesia may be prolonged.[17]

The selection of anesthetic agents is very important to adjust the postoperative recovery time in daily dental treatments planned under general anesthesia. While intravenously administered agents such as propofol, ketamine, thiopental and midazolam are generally preferred as anesthetic agents, sevoflurane is the most preferred among inhalation agents.[18] However, short-acting opiates such as alfentanil and remifentanil are recommended for analgesia during the operation.[19] In this study, the remifentanil-propofol combination was the most preferred anesthetic agent among the intravenous anesthetic agents, while the sevoflurane-oxygen combination was used among the inhalation agents.

When the dental treatments performed in this study were evaluated, it was seen that restorative treatments and tooth extraction were more common than other treatments, while fissure sealant and pulp treatments were less frequent. A review stated that restorative treatment and tooth extractions are more common in dental procedures performed under general anesthesia than other treatments.[7] In a similar study, it was observed that restorative treatment and tooth extraction were more preferred.[20] In a study evaluating dental treatments performed under general anesthesia, it was observed that restorative and endodontic treatments were preferred[21]. However, in this study, pulp treatments, which may have a high risk of post-operative complications and failure and may require patients to undergo re-anesthesia, were less preferred than other treatments. In a study, it was reported that in cases where fissure sealant, which is one of the preventive applications, is used less frequently, the need for dental treatment under general anesthesia arises again.[22] In this study, fissure sealant was used less frequently than other treatments. This can be explained by the fact that the majority of patients are individuals with special needs and cavitations often occur in the teeth along with poor oral hygiene.

The use of analgesia after dental treatments are performed under sedation and general anesthesia varies depending on the type and size of the treatment. While local infiltration anesthesia was sufficient for analgesia in 18.1% of the patients, paracetamol was used together with infiltration anesthesia in 81.9%. There is a risk of toxicity when a sufficient dose of local infiltration anesthesia is used in patients undergoing multiple tooth extraction. To avoid this risk, an-

algesia management was performed using paracetamol.

5. Conclusion

Dental general anesthesia and sedation applications, which have become increasingly popular lately, allow all treatments to be performed successfully in a single session. In order to minimize the risk of anesthesia in young children and individuals with special needs, pre-anesthesia evaluation and planning should be done in detail. When we look at dental treatments, it is seen that physicians are torn between radical and conservative approaches and there is no consensus on this issue in the literature. In this case, dental treatment approaches should be decided by taking into consideration the operating conditions, the general and oral health of the patient, and the wishes of the parents.

Conflict of interest statement

The authors wish to state that they have no financial interests related to the content of this report.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved *Cukurova University Hospital Ethics Commitee for this study (Decision No: 2023-133-53)*

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Availability of data and materials

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

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Comparison of De Ritis Rate for Del Nido Versus Blood Cardioplegia in Patients Who Underwent Coronary Artery Bypass Graft Under Cardiopulmonary Bypass

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Abstract

Aim: Within the scope of this research, we aimed to compare the liver function tests, liver enzymes and De Ritis ratio of patients given Del Nido cardioplegia and blood cardioplegia in coronary heart surgery.

Methods: This retrospective study included a total of 80 patients who underwent cardiopulmonary bypass (CPB) guided coronary heart surgery with 40 Del Nido cardioplegia solutions and 40 blood cardioplegia solutions. CPB-guided coronary heart surgery patients given Del Nido cardioplegia solution were determined as the first group (Group 1), and patients given blood cardioplegia were determined as the second group (Group 2).

Results: Preoperative and postoperative aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, and gamma-glutamyl transferase (GGT) levels of the groups were similar (p>0.005). AST, ALT, total bilirubin, direct bilirubin, and GGT levels were similar in CPB output (p>0.005). The De Ritis ratio of the groups was similar on the preoperative and postoperative 1st day (p=0.072; p=0.687, respectively), and the rate of ritis at CPB output was higher in group 2 (p=0.003). The requirement for defibrillation was higher in group 1 (p=0.044).

Conclusions: The Del Nido cardioplegia solution may be superior to blood cardioplegia in coronary artery bypass graft (CABG) cases accompanied by CPB regarding the De Ritis ratio.

Keywords: *Cardiopulmonary bypass, coronary artery bypass graft, del nido cardioplegia, blood cardioplegia, de ritis rate*

1. Introduction

Myocardial protection during diastolic arrest and cardiopulmonary bypass (CPB) in cardiac surgery has been an important area of interest. However, the optimal cardioprotective strategy and ideal cardioplegia solution are still debated. Cardioplegia is an integral method of myocardial protection, which is required to prevent cardiac arrest in open-heart surgery[1]. The immobile heart reduces the likelihood of air embolism during open procedures on the left side of the heart and provides a surgical space. Cross-clamping eliminates continuous coronary blood flow to the myocardium, providing a bloodless surgical field and increasing visibility[2, 3]. Del Nido cardioplegia in adults as a single dose prevents interruption of the surgery. It has been reported that intraoperative peak glucose value surgery, shortening cross-clamp time, duration of CPB, and total and insulin requirement are lower with Del Nido cardioplegia, which has prognostic importance. Additionally, this technique has a lower incidence of atrial fibrillation (AF) and a decrease in the need for defibrillation[4]. Del Nido cardioplegia involves a base Plasma-Lyte A solution with an electrolyte composition similar to an extracellular fluid[5]. It is delivered with 20% by volume of fully oxygenated patient blood, which supports aerobic metabolism for a limited period and provides buffering properties to promote anaerobic glycolysis[6].

Blood cardioplegia is achieved by adding autologous patient blood taken from the cardiopulmonary bypass circuit to crystalloid cardioplegia solution in different ratios (8:1, 4:1, 2:1). The advantages of blood cardioplegia include providing an oxygenated environment, limiting haemodilution, having high buffering capacity, having ideal osmotic properties, and having many endogenous antioxidants[7].

Liver function abnormalities are common in heart failure patients. In the past, increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values in heart failure patients were attributed to low perfusion. In contrast, the decreased AST/ALT ratio was attributed to damage secondary to increased venous congestion observed in heart failure. Hence, the De Ritis ratio (AST/ALT ratio) may be utilized as a predictive marker in cardiac events such as heart failure, acute coronary syndromes, and acute myocardial

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infarction[8–10]. Additionally, a high De Ritis ratio was reported as an independent risk factor of mortality and adverse cardiovascular events in coronary artery disease patients[9, 10].

The plasma AST and ALT levels are within normal limits in the healthy population. These parameters are usually affected in chronic hepatitis, coronary heart disease, impaired renal function, and due to several medications. The previous literature elaborated that it is more convenient to calculate both AST and ALT as a composite parameter rather than using any single of them.

Within the scope of this research, we aimed to compare the liver function tests, liver enzymes and De Ritis ratio of patients given Del Nido cardioplegia and blood cardioplegia in coronary heart surgery (Coronary artery bypass graft – CABG).

2. Materials and methods

This study is a retrospective cohort clinical study.

2.1. Ethics Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. In this study; before the study, approval was obtained from the institution where the study will be conducted (Şanlıurfa Mehmet Akif İnan Training and Research Hospital) and the local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 10.04.2023 - Approval no: HRÜ/23.06.04). As this was retrospective research, no informed consent has been obtained from participants.

2.2. Population of the Research

In this study, retrospectively, CPB-guided coronary heart surgery (CABG replacement) was performed between 01/04/2022-01/04/2023, and after applying the exclusion criteria, 80 patients, for whom 40 del nido cardioplegia solutions and 40 blood cardioplegia solutions were used, were consecutive sequential included.A website was used to calculate the sample size of the groups https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html). The type I error rate was accepted as a maximum of 5 %, while the type II error rate was accepted as a maximum of 20 %. The effect size of the study was determined as ≥0.5.CPB-guided coronary heart surgery patients given Del Nido cardioplegia solution were determined as the first group (Group 1), and patients given blood cardioplegia were determined as the second group (Group 2).Demographic data, preoperative, intraoperative, and early postoperative data of the patients were obtained from the hospital database.

2.3. Exclusion and Inclusion Criteria

Patients with medication use or treatment that may affect liver enzymes before surgery (i.e. cholesterol and antifungal medications, some rheumatism medications, antibiotics such as tetracycline, cortisone, some depression medications and simple painkillers containing paracetamol), chronic liver patients, AF history, those with heart valve pathology, those with aortic valve insufficiency or stenosis, those with mitral valve insufficiency or stenosis, those with known systemic inflammatory disease, those who underwent emergency surgery or re-operation, and chronic hemodialysis patients were excluded from the study. After applying the exclusion criteria, consecutive patients who underwent CPB-guided isolated CABG replacement surgery were included in the study.

2.4. Surgical Approach

Standard coronary heart surgery techniques were implemented. Following median sternotomy, arterial cannulation was performed through the ascending aorta, and venous cannulation was performed through a single venous two-stage venous cannula from the right atrium. The left mammary artery graft was utilized in all cases. A saphenous vein was applied to other coronary grafts. All patients underwent complete revascularization.

2.5. Cardiopulmonary Bypass (Perfusion) Method

Patients' blood flow rates during extracorporeal circulation were determined according to body surface areas (2.4 L/min/m2). An oxygenator and tubing set suitable for the patient's weight and appropriate cannula diameters according to body surface areas were used. Membrane oxygenator/tubing sets with integrated arterial filters were used. Tubing set venous line diameter was used as 1/2, and the arterial line diameter was used as 3/8. A 32oC hypothermia was applied to all patients during extracorporeal circulation. Arterial line pressures were maintained on average between 150–180 mmHg during CPB. By providing adequate anticoagulation, the active clotting time (ACT) was kept at 480 seconds and above, and 1200 mL of balanced solution (isolyte), 150 mL of 20 % mannitol, 5000 units of heparin and 2 g of cefazolin were used as the primarily.

2.6. Blood Cardioplegia Solutions

An isothermic blood cardioplegia solution (32oC) was used. The initial cardioplegia dose was 15 mL/kg (full dose) as the solution amount, and maintenance doses were administered as half dose every 20 minutes. Full dose (first dose) cardioplegia solution was prepared by adding 7.5 % potassium chloride (patient's blood gas K+ value + K+ mL to be added = 25 mL), 5 mL 15 % magnesium sulfate, 10 mL 8.4 % sodium bicarbonate into oxygenated patient blood. 7.5 % potassium chloride (patient's blood gas K+ value + K+ mL to be added = 7 mL), 5mL of 15 % magnesium sulfate, and 5mL of 8.4 % sodium bicarbonate were added to the oxygenated patient blood in maintenance doses.

2.7. Del Nido Cardioplegia Solution

Modified Del Nido cardioplegia solution was used at +4 oC. A single dose as the solution amount was used as 20 mL/kg with a maximum dose of 1000 mL. In cases with aortic cross-clamp (ACC) time of more than ninety minutes, a maintenance half dose was administered at 60 minutes. The solution was prepared by adding 17 mL 20% mannitol, 14 mL 15 % magnesium sulfate, 13 mL 8.4 % sodium bicarbonate, 27 mL 7.5 % potassium chloride, and 6.5 mL 2 % Lidocaine into a balanced isolating solution (ratio: 8/10) and oxygenated patient blood (ratio: 2/10).

2.8. Statistical Analyses

Patient data collected within the scope of the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data mean, and standard deviation for continuous data were given as descriptive values. For comparisons between groups, the “Independent Sample T–test” was used for two groups, and the “Pearson Chi-Square Test” was used to compare categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

3. Results

The demographic and intraoperative data of the groups: age, gender, number of CABG, height, weight, body surface area (BSA), flow, perfusion time, aortic cross clamp (ACC) time, ejection fraction (EF) percentage, fluid given during CPB, amount of urine during CPB, erythrocyte suspension (ES) transfusion during CPB, extubation time, length of stay in the intensive care unit (ICU) and length of hospital stay were similar (p>0.005) (Table 1).

The preoperative AST, ALT, total bilirubin, direct bilirubin and gamma glutamyl transferase (GGT) levels of the groups were similar and there was no statistically significant difference between the groups (p=0.651; p=0.751; p=0.421; p=0.053; p=0.585, respectively) (Table 2). AST, ALT, total bilirubin, direct bilirubin and GGT levels measured at CPB output of the groups were similar and

there was no statistically significant difference between the groups (p=0.676; p=0.075; p=0.663; p=0.305; p=0.735, respectively) (Table 2).

Table 1

Comparison of demographic, preoperative, intraoperative and postoperative parameters of the groups

		Group-1 (N=40)	Group-2 (N=40)	p
Age (years) (Mean±SD)		60.75±9.60	61.87±8.54	0.462
Gender (n, %)	Female	19, (47.5%)	22, (55%)	0.675
	Male	21, (52.5%)	18, (45%)	
Number of CABGs (n, %)	I	2, (5%)	2, (5%)	0.857
	II	8, (20%)	6, (15%)	
	III	17, (42,5%)	17, (42,5%)	
	IV	13, (32.5%)	15, (37.5%)	
Height (cm) (Mean±SD)		165.42±8.85	165.35±9.20	0.692
Weight (kg) (Mean±SD)		79.02±13.33	79.47±12.66	0.880
BSA (m2) (Mean±SD)		1.88±0.18	1.89±0.17	0.810
Flow (L) (Mean±SD)		4.53±0.42	4.49±0.39	0.718
Perfusion Time (min) (Mean±SD)		102.75±29.48	110.48±45.74	0.154
ACC Time (min) (Mean±SD)		79.42±31.32	81.75±35.01	0.399
EF% (Mean±SD)		50.80±7.84	50.65±7.68	0.853
Delivered Liquid (ml) (Mean±SD)		2221.40±521.18	2064.60±660.97	0.307
Urine Amount (ml) (Mean±SD)		1893.80±411.87	1658.80±575.89	0.162
Int. Blood Trans. (unit) (Mean±SD)		1.05±1.15	1.30±1.26	0.196
Extubation Time (Hour) (Mean±SD)		6.52±2.02	6.45±2.67	0.244
ICU Time (days) (Mean±SD)		3.10±0.96	3.05±1.06	0.482
Length of hospital stay (Mean±SD)		9.37±3.25	9.32±3.39	0.581

Mean±SD: Mean±standard deviation; n, %: number, percentage; CABG: Coronary artery bypass graft; BSA: Body surface area; ACC: Aortic cross-clamp; EF %: Ejection fraction percentage; Int. Blood Trans.: Intraoperative blood transfusion; ICU: Intensive care unit.

Table 2

Comparison of preoperative, intraoperative and postoperative parameters of the groups

	Group-1 (N=40) (Mean±Sd)	Group-2 (N=40) (Mean±Sd)	p
Preoperative AST	23.92±14.58	23.24±15.58	0.651
Preoperative ALT	30.74±20.48	27.51±20.18	0.751
Preoperative Total Bilirubin	0.53±0.29	0.52±0.23	0.421
Preoperative Direct Bilirubin	0.18±0.09	0.92±0.71	0.053
Preoperative GGT	37.65±34.91	33.65±33.79	0.585
CPB Output AST	27.00±13.29	24.76±13.93	0.676
CPB Output ALT	68.32±67.43	51.62±34.02	0.075
CPB Output Total Bilirubin	0.65±0.35	0.64±0.36	0.663
CPB Output Direct Bilirubin	0.18±0.18	0.21±0.19	0.305
CPB Output GGT	29.75±21.37	27.25±21.53	0.735
Postoperative Day 1 AST	53.70±77.58	41.77±59.83	0.228
Postoperative Day 1 ALT	117.70±218.94	85.74±161.88	0.127
Postoperative Day 1 Total Bilirubin	1.04±1.11	0.94±0.82	0.208
Postoperative Day 1 Direct Bilirubin	0.51±0.68	0.45±0.47	0.273
Postoperative Day 1 GGT	36.52±21.67	31.47±18.25	0.214

Mean±SD: Mean±standard deviation; n, %: number, percentage; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase.

AST, ALT, total bilirubin, direct bilirubin and GGT levels measured at CPB output of the groups were similar and there was no statistically significant difference between the groups (p=0.228; p=0.127; p=0.208; p=0.273; p=0.214, respectively) (Table 2).

The AST/ALT ratio of the groups was similar on the preoperative and postoperative 1st day, and there was no statistically significant difference between the groups (p=0.072; p=0.687, respectively) (Figure 1). The rate of De Ritis ratio was higher in the CPB output in group 2, with a statistically significant difference (p=0.003) (Figure 1). Perioperative pacemaker requirement, inotropic requirement, intra-aortic balloon pump (IAPP) requirement, acute renal failure (ARF), and mortality rates of the groups were similar (p=0.244; p=0.139; p=1.000; p=0.139; p=1.000, respectively). However, the need for defibrillation was higher in group 1 (p=0.044) (Table 3).

Table 3

Comparison of ritis rates and perioperative outcomes of the groups

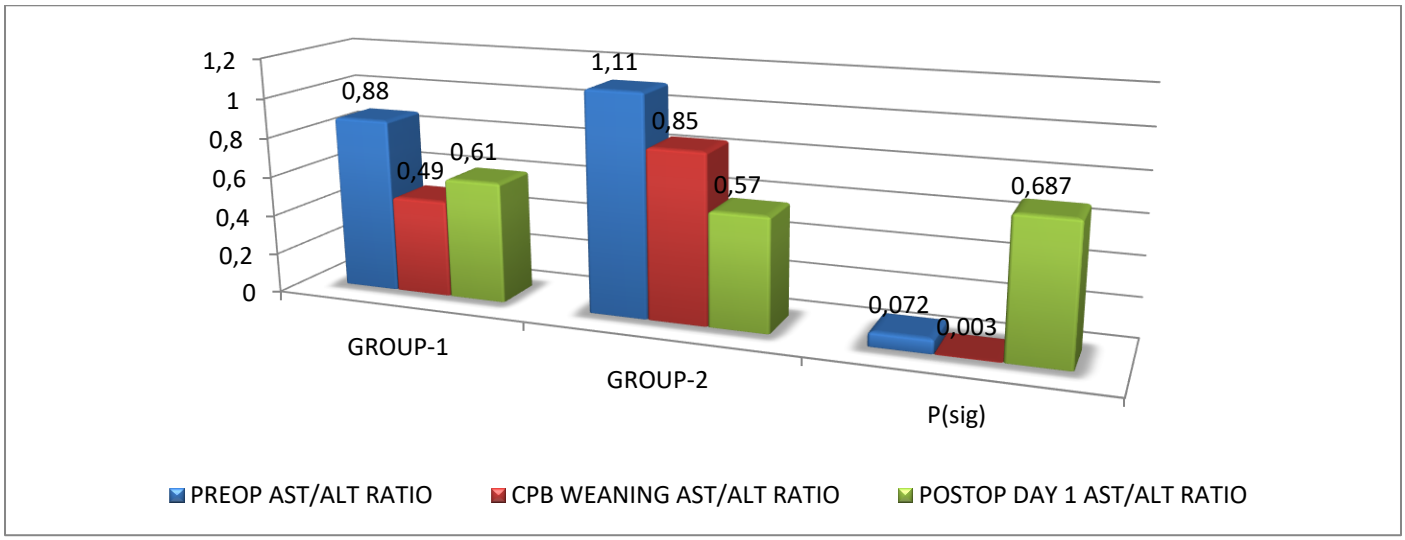
		Group-1 (N=40)	Group-2 (N=40)	p
Preoperative AST/ALT Rate (Mean±SD)		0.88±0.44	1.11±1.15	0.072
CPB Output AST/ALT Rate (Mean±SD)		0.49±0.18	0.85±1.23	0.003
Postoperative Day 1 AST/ALT Rate (Mean±SD)		0.61±0.25	0.57±0.25	0.687
Pacemaker Requirement, (n, %)	• Yes	2, (5%)	1, (2.5%)	0.244
	• No	38, (95%)	39, (97.5%)	
Defibrillation Requirement, (n, %)	• Yes	18, (45%)	13, (32.5%)	0.044
	• No	22, (55%)	27, (67.5%)	
Inotrope Requirement, (n, %)	• Yes	37, (92.5%)	35, (87.5%)	0.139
	• No	3, (7.5%)	5, (12.5%)	
IABP Requirement, (n, %)	• Yes	1, (2.5%)	1, (2.5%)	1.000
	• No	39, (97.5%)	39, (97.5%)	
ARF, (n, %)	• Yes	5, (12.5%)	3, (7.5%)	0.139
	• No	35, (87.5%)	37, (92.5%)	
Mortality, (n, %)	• Yes	0, (0%)	0, (0%)	1.000
	• No	40, (100%)	40, (100%)	

Mean±SD: Mean±standard deviation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CPB: Cardiopulmonary bypass; IABP: Intra-aortic balloon pump; ARF: Acute renal failure.

4. Discussion

The AST/ALT ratio is also associated with an increased risk of cardiovascular disease. It can also be used as a simple independent determinant of left ventricular functional status in patients with heart failure and reduced ejection fraction. Furthermore, after the risk factors are eliminated, a high AST/ALT ratio can be evaluated as an independent indicator of future cardiovascular mortality[11]. In this research, AST/ALT was compared to evaluate the superiority or equivalence of two different cardioplegia solutions and was similar on the preoperative and postoperative 1st day in the patient groups who underwent both cardioplegia methods. At CPB output, it was observed that AST/ALT was significantly higher in the blood cardioplegia group. This suggested that Del Nido cardioplegia might be superior to blood cardioplegia. In addition, the results of liver function tests (AST, ALT) and liver enzymes (total bilirubin, direct bilirubin and GGT) at different times were similar in the two groups. Nonetheless, examining the perioperative results, it was observed that the required for intracardiac defibrillation was significantly higher in the group using Del Nido cardioplegia. Several studies indicated that each of the liver aminotransferases was inversely and independently associated with the risk of cardiovascular disease. It was also stated that it did not provide a significant improvement in the risk assessment of cardiovascular diseases beyond traditional cardiovascular disease risk factors[12].

Figure 1
Graphical analysis of the ritis rates of the groups



These results could be interpreted as the advantages of the study.
The AST/ALT ratio was indicated as a risk factor for cardiovascular diseases in previous literature[13]. In one of these studies, the correlation between AST/ALT ratio and peripheral arterial disease (PAD) was investigated in the hypertensive population. In their study, they analyzed the data of 10.900 patients with hypertension and found that 350 (3.2 %) of these patients had PAD. The risk of PAD increased with the AST/ALT ratio. Additionally, a higher AST/ALT ratio (≥1.65) was associated with the risk of PAD in Chinese adults with hypertension. This led to the idea that a high AST/ALT ratio could be an appropriate, cost-effective, and beneficial tool for assessing the risk of atherosclerosis[14]. In our study, we used AST/ALT as a marker for postoperative results in cardiac surgery using two different cardioplegia solutions.
In another study, it was stated that the elevated AST/ALT ratio was associated with all-cause death and cancer. Chen W. et al.[15] investigated the correlation of the AST/ALT ratio as a possible determinant of mortality and cancer incidence. They found that both serum ALT and AST levels increased in patients with chronic disease, but the AST/ALT ratio decreased in general. In that study, they also claimed that cancer cases had a higher baseline rate (median = 1.15, IQR: 0.91-1.44) than non-cancer cases (median = 1.23, IQR: 0.96-1.54). They reported that a high AST/ALT ratio increased the risk of all-cause mortality. Thus, the AST/ALT ratio may be a potential biomarker for evaluating healthy conditions and long-term mortality, especially for cancer and its prognosis[15]. These findings indicated Del Nido cardioplegia might be a safer alternative than blood cardioplegia. Zhou J. et al.[16] investigated the AST/ALT ratio as an important determinant of prostate cancer incidence and found that the increased AST/ALT ratio predicted increased cancer incidence[16]. However, controversial data exists in the literature[17].
Liver function enzymes such as AST and ALT could be utilized as biomarkers that reflect disease severity in several chronic liver diseases. More recently, Weng SF et al.[18] reported that high AST/ALT ratios were independently associated with an increased risk of developing cardiovascular disease in men within ten years but not in women. They also stated that the AST/ALT ratio provides greater benefits in predicting cardiovascular diseases in individuals with high ALT levels[18]. These data supported our outcomes. Weng SF et al.[18] also concluded that the AST/ALT ratio should not be included in risk estimation tools in cardiovascular diseases. Furthermore, they stated that those with a high AST/ALT ratio may represent a higher risk that may be beneficial, especially when ALT is elevated, which may lead to the assumption that Del Nido cardioplegia is superior.
Liu Y. et al.[19] investigated the relationship between AST/ALT ratio and arterial stiffness in a cross-sectional study in a Japanese population without fatty liver. In their study, they observed that the relationship between AST/ALT ratio and arterial stiffness was not linear. However, an AST/ALT ratio greater than 13.1 (per 0.1 change) was positively associated with arterial stiffness[19]. Feng X. et al.[20] investigated the relationship between AST/ALT ratio and cardiovascular disease mortality in peritoneal dialysis patients. They found that peritoneal dialysis patients with high AST/ALT ratio levels might be at a significant risk of cardiovascular disease mortality[20]. In our study, since the CPB output AST/ALT ratio was higher in the blood cardioplegia group, Del Nido cardioplegia was considered superior.
Studies on GGT reported that GGT levels did not provide promising results in predicting the first cardiovascular events[21]. However, the fact that the two cardioplegia solutions were similar in comparing perioperative outcomes, our study suggested that the two cardioplegia solutions might have similar results.
When evaluating the two cardioplegia solutions in terms of perioperative results, it is possible to say that Del Nido cardioplegia is superior when we consider the value of the De Ritis rate, which is a predictor for liver damage, at the time of CPB exit, while the need for defibrillation is disadvantageous in the Del Nido cardioplegia solution group. In addition, in clinical use, the fact that del Nido cardioplegia is a single dose (additional half dose if needed), whereas blood cardioplegia requires administration every twenty minutes may cause a separate loss of time for the surgical team, interrupting the operation and prolonging the duration of CPB, and is a disadvantage in terms of a separate workload for the perfusionist. However, when evaluated in terms of liver function tests and liver enzymes, it can be considered that the two cardioplegia methods show equivalent results.

4.1. Limitations of the Study

The limitations of this study are that it is single-centered and retrospective. Moreover, only the cases with CABG replacement were in-

cluded in our study. We believe that the inclusion of more multi-center groups with different cardiac diagnoses and more patients in the study will yield more comprehensive results.

5. Conclusion

According to the results of this study, the effects of Del Nido cardioplegia solution and blood cardioplegia on liver function tests and liver enzymes were similar in CABG performed under CPB guidance. However, AST/ALT ratio at CPB discharge was higher in the blood cardioplegia group; therefore, del Nido cardioplegia may be considered superior to blood cardioplegia. The need for intracardiac defibrillation was a disadvantage for del Nido cardioplegia. In conclusion, although the effects of the two cardioplegia solutions on the liver showed similar results, del nido cardioplegia may be superior in terms of De Ritis rate.

Statement of ethics

In this study; before the study, approval was obtained from the institution where the study will be conducted (Sanliurfa Mehmet Akif Inan Training and Research Hospital) and the local ethics committee (Harran University Clinical Research Ethics Committee) (Date: 10.04.2023 - Approval no: HRÜ/23.06.04). As this was retrospective research, no informed consent has been obtained from participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

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

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Consent for publication

The original article is not under consideration by another publication, and its substance, tables, or figures have not been published previously and will only be published elsewhere.

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Exploring the Complex Relationship Between Primary Headache Types and Bruxism: Patterns, Mechanisms, and Implications

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Abstract

Aim: The present study aims to explore the relationship between primary headache types and bruxism and determine how these two conditions may affect each other.

Methods: A total of 97 cases who applied to the Neurology Polyclinic of our hospital during 01.07.2023-01.08.2023 were included in the study. A comprehensive questionnaire was applied to the participants. The diagnosis of headache was established based on the International Classification of Headache Disorders criteria; the American Academy of Sleep Medicine criteria were used for the diagnosis of sleep bruxism and the Research Diagnostic Criteria for Temporomandibular Disorders were employed for the diagnosis of awake bruxism.

Results: Nineteen (19.6%) of the participants were male and 78 (80.4%) were female. Tension-type headache (TTH) was reported by 22 participants (22.7%), 30 participants had migraine-type headache (30.9%), and 45 participants (46.4%) comprised the healthy control group. Sleep bruxism was observed in 29 patients (29.9%), while 11 patients (11.3%) were diagnosed with awake bruxism. Higher rates of sleep bruxism and awake bruxism were seen in patients in the TTH group compared to those in the migraine group and the healthy control group ($p<0.001$; $p<0.001$, respectively).

Conclusions: This study provides a significant contribution to the understanding of the relationship between primary headache types and bruxism. Forming a basis for future research, our findings highlight the need for a comprehensive evaluation of these two conditions.

Keywords: *Bruxism, primary headache disorders, migraine disorders, tension-type headache*

1. Introduction

In 2013, an international group of bruxism experts held a written consensus discussion to formulate and ensure functionality of the definition of bruxism. In this context, bruxism was defined as repetitive masticatory muscle activity characterized by clenching or grinding of the teeth and/or supporting or pushing the lower jaw.[1] Following this definition, an international consensus meeting referred to as the Assessment of Bruxism Status was held in 2017 with the participation of bruxism experts across the globe to discuss the shortcomings encountered in clinical practice and studies in this field. This meeting resulted in bruxism no longer being defined under a single umbrella term, and two separate definitions were made, namely sleep bruxism and awake bruxism.

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Sleep and awake bruxism were defined as masticatory muscle activities that occur during sleep (characterized as rhythmic or non-rhythmic activity) and wakefulness (characterized by repetitive or continuous tooth contact and/or supporting or pushing the lower jaw), respectively. The meeting also concluded that bruxism in healthy subjects should not be considered a disease but a behavior that may be a potential risk factor for certain clinical outcomes.[2]

Headaches are considered a symptom of bruxism. According to a study by Costa et al. (2008), bruxism is mostly reported by patients who have headaches and 71.4% of patients with headache complaints have bruxism.[3] Headache has a significantly negative impact on quality of life. Almost all patients living with migraine and 60% of those with tension-type headache (TTH) are known to experience reduced work capacity and less participation in social activities. TTH and migraine are recognized as neurological disorders due to their high prevalence worldwide.[4] The current literature on these two types of primary headache (TTH and migraine) suggests that psychosocial factors that may behaviorally manifest as bruxism may be associated with the increased prevalence of these headaches as well as dysfunction in the masticatory and cervical muscles.[5] Alt-

hough previous studies have intensively discussed the relationship between bruxism and primary headache, these studies typically have low levels of evidence and highly different methodologies.[6]

The main purpose of the present study is to explore the relationship between headache types and bruxism in greater detail and understand the mechanisms underlying this relationship. We believe that the results of our study will provide an important contribution in improved understanding of the relationship between primary headache types and bruxism and evaluation of how these two conditions may affect each other.

2. Materials and methods

Patients between the ages of 18-50 with tension-type or migraine headache who applied to the Neurology Outpatient Clinic of our hospital during 01.07.2023-01.08.2023 and who were able to understand and answer the questionnaire questions as well as a group of healthy subjects were included in the study. Prior to the study, The Clinical Trials Ethics Committee of our hospital granted approval for the conduct of this study (approval number: 2627, date: 08.06.2023).

All subjects were asked questions about age, gender, education level, type of headache; examined for temporomandibular hypertrophy/tenderness; and a research questionnaire was applied to the participants.

The questionnaire used in this study consisted of the following questions:

1. Does another person sleep in the same room where you sleep?
2. Has anyone ever told you that you grind your teeth in your sleep?
3. Do you ever wake up to find your jaw locked or your lower jaw clenched forward?
4. Do you feel pain or stiffness in your jaw muscles when you wake up?
5. How often do you clench your teeth during sleep (is it more than 5 times a week?)
6. How often do you grind your teeth during sleep (is it more than 5 times a week?)
7. How often do you clench your teeth when you are awake (is it more than 5 times a week?)
8. How often do you grind your teeth when you are awake (is it more than 5 times a week?)

All participants answered these questions as 'yes' or 'no'. The diagnosis of sleep bruxism was made by a neurologist according to the American Academy of Sleep Medicine (AASM)[7] guideline, which has a validated Turkish translation, and the diagnosis of primary headache was made based on the International Classification of Headache Disorders (ICHD-3)[8] diagnostic criteria. The Turkish translation of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) questionnaire[9] was used for the diagnosis of wakefulness bruxism. Patients who answered 'yes' to RDC/TMD question 15d, "Do you grind or clench your teeth during the day?" were diagnosed with awake bruxism. Patients with alcohol and caffeine addiction, those with sleep disorders and psychiatric conditions, those using anti-migraine or antidepressant medication, and those using drugs that may cause bruxism were excluded from the study.

2.1. Statistical analysis

The SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages whereas continuous measurements were summarized as mean values and standard deviation (with median and minimum-maximum values where necessary). The chi-square test was used for the comparisons of categorical variables. The Shapiro-Wilk test was employed to determine whether the parameters in the study showed normal distribution. The Kruskal-Wallis test was used for parameters that did not show normal distribution. Statistical significance level was considered 0.05 in all tests.

3. Results

The mean age of the participants was 32.6±10.9 years; 19 (19.6%) were male and 78 (80.4%) were female. Twenty-eight (28.9%) of the cases had primary education, 32 (33.0%) had graduated high school and 37 (38.1%) had a bachelor's degree.

Twenty-two (22.7%) of the cases had TTH, 30 (30.9%) suffered from migraine headaches, and 45 (46.4%) were in the healthy control group. Age, gender and education status were found to be similar across the groups (p>0.05).

Sleep bruxism was observed in 29 (29.9%) of the patients, while 11 (11.3%) patients were diagnosed with awake bruxism. We observed that 29.5% of female patients had sleep bruxism and 31.6% of male patients had sleep bruxism. Awake bruxism was present in 9% of female participants and 21.1% of male participants **(Fig. 1)**. The presence of sleep bruxism and awake bruxism did not differ by gender (p=0.85; p=0.13, respectively). Higher rates of sleep bruxism and awake bruxism were seen in patients in the TTH group compared to those in the migraine group and the healthy control group (p<0.001; p<0.001, respectively).

The proportion of participants who reported teeth grinding during sleep was higher in the TTH and migraine groups than that in the healthy control group (p=0.006). The proportion of those who felt pain or stiffness in the jaw muscles upon waking up in the morning was higher in the TTH and migraine groups compared to the healthy control group (p<0.006). The rate of clenching and grinding of teeth more than 5 times a week during sleep was significantly higher in the TTH group compared to the other two groups (p=0.002; p=0.007, respectively). The rate of clenching and grinding of teeth more than 5 times a week during wakefulness was significantly higher in the TTH group compared to the other groups (p<0.001; p=0.001, respectively) (Table 1).

Figure 1

Gender distribution according to bruxism type.

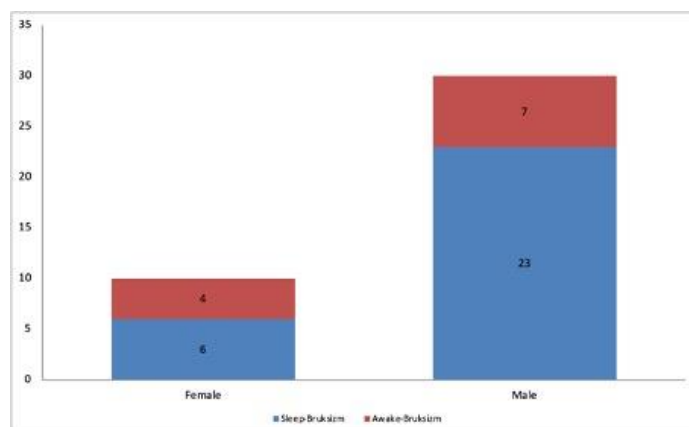

Table 1
Demographic characteristics of the groups

	TTH (n=22)	Migraine (n=30)	Healthy Controls (n=45)	p
	n (%)	n (%)	n (%)	
Age (median [IQR])	27.5 (20)	32 (13)	31 (18)	0.737‡
Gender				
• Male	6 (27.3)	2 (6.7)	11 (24.4)	0.096†
• Female	16 (72.7)	28 (93.3)	34 (75.6)	
Education status				
• Primary education	7 (31.8)	13 (43.3)	8 (17.8)	0.142†
• High school	8 (36.4)	6 (20)	18 (40)	
• University	7 (31.8)	11 (36.7)	19 (42.2)	
Pain/tenderness in the temporomandibular joint	20 (90.9)	13 (43.3)	8 (17.8)	<0.001**,†
Has anyone ever told you that you grind your teeth in your sleep?	6 (27.3)	7 (23.3)	1 (2.2)	0.006**,†
Do you ever wake up to find your jaw locked or your lower jaw clenched forward?	10 (45.5)	8 (26.7)	2 (4.4)	<0.001**,†
Do you feel pain or stiffness in your jaw muscles when you wake up?	15 (68.2)	15 (50)	7 (15.6)	<0.001**,†
How often do you clench your teeth during sleep (is it more than 5 times a week)?	6 (27.3)	4 (13.3)	-	0.002**,†
How often do you grind your teeth during sleep (is it more than 5 times a week)?	5 (22.7)	4 (13.3)	-	0.007**,†
How often do you clench your teeth when you are awake (is it more than 5 times a week)?	9 (40.9)	2 (6.7)	-	<0.001**,†
How often do you grind your teeth when you are awake (is it more than 5 times a week)?	5 (22.7)	1 (3.3)	-	0.001**,†
SB	15 (68.2)	10 (33.3)	4 (8.9)	<0.001**,†
AB	9 (40.9)	2 (6.7)	-	<0.001**,†

** p<0.05, **p<0.001, †: Chi-square test, ‡: Kruskal-Wallis test*
TTH: Tension-type headache, SB: Sleep bruxism, AB: Awake bruxism

4. Discussion

In this study, we found a significant relationship between primary headache and bruxism. The analysis by primary headache subtypes revealed a significantly higher rate of bruxism in the TTH group compared to the migraine group.

As typically seen in studies on headaches, the majority (80.4%) of our study sample consisted of females. [10,11] The fact that women often have greater health awareness and more regular access to healthcare services than men may partially explain this dominance. On the other hand, the presence of bruxism did not appear to differ by gender in our study cohort. This finding is consistent with the results reported by Melis et al. [12] and Manfredini et al. [13] The authors of a systematic review reported a higher frequency of bruxism in female patients compared to males [14], whereas Lukomska-Szymanska et al. [15] reported male predominance in a cohort of 1900 patients. These conflicting findings may be resulting from the complex etiology of bruxism as well as the involvement of various factors in the development of bruxism. Furthermore, the fact that this relationship has not been associated with gender suggests that bruxism may in fact be a common problem in the general population.

In a recent study, Mihaiu et al. (2023) reported bruxism in 86% of 67 patients with primary headache. [5] They also reported high levels of stress and anxiety in these patients, which is consistent with the relevant literature. [16,17] Similarly, we observed bruxism in 77% of 52 patients with primary headache in our study. We did not use a specific scale to determine the psychiatric comorbidities of the patients included in our study; however, the presence of a control group and the classification of primary headache syndromes and bruxism according to their subtypes are the strengths of our study. Muayqil et al. (2018) examined 3,853 patients and reported a higher rate of bruxism in 1,333 patients with migraine compared to the non-headache group. [18] Analyzing 400 medical records, Porporatti et al. (2015) showed that self-reported bruxism was not associated with the presence of primary headache (TTH or migraine). [19] Fernandes et al. (2013) [20] & Wagner et al (2018) [21] reported that sleep bruxism alone does not increase the risk of any primary headache; however, the likelihood of migraine and tension headache may increase significantly when associated with a painful temporomandibular disorder (TMD). A strong relationship between sleep bruxism and tension-type headache was reported by Mihaiu et al. (2023) in a cohort of 67 cases. They also showed that waking bruxism was associated with both TTH and migraine headaches. [5] The authors highlighted that this difference could be explained by the fact that continuous teeth clenching during the day maintains a high level of tension in masticatory muscles, leading to increased sensitivity of the nociceptors of peripheral muscles and a change in the stimulus-response function over time. In a study of 307 medical records, Silva et al. (2022) reported a 2.27-fold increased likelihood of awake bruxism (AB) in subjects suffering from headaches. In their study, participants with self-reported AB were more likely to report headache and vice versa, as participants who reported headache were more likely to have AB. [22] In our study, AB was present in 11.3% of the patients with headache and we did not observe AB in the non-headache group. A strength of our study is that the diagnosis of headache was based on the ICHD-3 criteria and not on a self-reported questionnaire such as the RDC/TMD. In a recent clinical study, Haggiag and Speciali (2020) reported a relationship between AB and chronic migraine. After treatment for AB using an intraoral appliance designed for daytime use, the patients reportedly achieved an improvement in pain severity, which was maintained at 1 year. [23]

Our study is not without limitations; firstly, we did not perform an objective evaluation of the participants in terms of temporomandibular joint disorders. However, on palpation, 63% of our patients had pain/sensitivity in the temporomandibular joint. Another limitation

is that we did not perform a polysomnographic examination for the definitive diagnosis of sleep bruxism. This would have been costly and inaccessible for such a large study sample as ours.

5. Conclusion

In conclusion, the present study provides a significant contribution to our understanding of the relationship between primary headache types and bruxism. Our results suggest that bruxism may occur through different mechanisms during the day and during sleep. This warrant further research examining the relationship between different forms of bruxism. In this context, we believe that the differences between the rates of sleep bruxism and awake bruxism need further detailed research to provide more greater insights on the potential of bruxism to trigger or exacerbate headaches. We also think that inquiring the complaints of bruxism in patients who presenting to the outpatient clinic with headache complaints and taking this into consideration in the treatment plan will increase the effectiveness of the treatment. Finally, further prospective studies on this subject may be advisable due to the conflicting literature reports on the relationship between bruxism and gender.

Statement of ethics

The study protocol was approved by the University of Health Sciences Turkey, Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 08.06.2023, Number: 2627)

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

Concept/Design: ZSŞ, EÇ; Analysis/Interpretation: ZSŞ, EÇ; Data Collection: ZSŞ, EÇ; Writer: ZSŞ; Critical Review: ZSŞ, EÇ; Approver: ZSŞ, EÇ All authors read and approved the final version of the manuscript.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Evaluating The Factors Affecting Mortality and Survival of the Patients Who Underwent Percutaneous Endoscopic Gastrostomy; The Short-term and Long-term Results

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Abstract

Aim: Percutaneous endoscopic gastrostomy (PEG) is a common minimally invasive technique performed in patients with oral feeding problems. The aim of the current study is to evaluate the associated factors that have an impact on the short- and long-term survival and mortality in these patients who received PEG tube placement.

Methods: The patients who underwent PEG placement between June 2020 and June 2023 are enrolled in the study. Mortality data was extracted from the National Death Registry database. Data regarding the demographics, indications of PEG, co-morbidities, length of hospital stay prior to PEG procedure, the need for mechanical ventilator support, body-mass index, serum levels of hemoglobin, leukocyte, albumin, and c-reactive protein are extracted retrospectively. Kaplan Meier and Cox regression analyses were used to evaluate the factors affecting survival.

Results: A total of 137 patients are enrolled in the study (71 female and 66 male). One-month mortality was 16.7% and overall mortality during a follow-up of 38 months was 51%. Survival was significantly higher in patients with motor neuron diseases than the patients with Alzheimer's (p=0.036). Length of hospital stay before PEG placement and haemoglobin levels were found to have a significant impact on survival in Cox regression analysis (p=0.000, p=0,009).

Conclusions: Length of hospital stay before PEG placement, need for mechanical ventilator support and hemoglobin levels were found significantly associated with survival. Higher mortality in Alzheimer's patients may indicate that indications of PEG should be re-evaluated in these patients.

Keywords: *Percutaneous endoscopic gastrostomy, survival, mortality*

1. Introduction

Advancements in healthcare have led to increased living standards and life expectancy, and together with reduced birth and death rates, resulted in an increased proportion of elderly individuals within the total population. Potential candidates for PEG placement appear to have doubled in recent years due to increased people with chronic diseases which is a direct consequence of the aging population.[1] Clinical utilization of PEG was initially reported in 1980.[2] PEG is a relatively simpler technique than traditional open surgical gastrostomy tube placement which has lower morbidity rates.[3]

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PEG is commonly indicated in patients in whom oral feeding is not expected to be restored for at least 4-6 weeks. Commonly, patients with cerebrovascular diseases, chronic neurological disease, cancer and chronic gastrointestinal disease are expected to benefit from PEG procedure.[4] Although the benefits of PEG were demonstrated in a certain subset of patients, increasing the incidence of PEG application raised some degree of concerns by some, and evidence about the long-term results is lacking.[5] The decision to place a PEG catheter is quite challenging for both the family members of the patients and the healthcare providers. A prominent theoretical benefit of feeding the patient with a catheter as perceived by the physicians and the patients' proxies is the improved survival.[6,7] However, current observational studies suggest that feeding catheters does not improve survival.[8,9] The poor results were attributed to the suggestion that these patients are referred too late to benefit from feeding by feeding tubes.[10]

In the present study, data from the patients who had undergone a

PEG procedure between June 2020 and June 2023 are retrospectively extracted to evaluate the prognosis of the patients. The primary aim of the study is to determine the factors that have an impact on mortality and survival in the short-term and long-term follow-up.

2. Materials and methods

A total of 137 patients are enrolled in the study. Local Ethical Board approval was obtained (Approval No: Samsun University KAEK-2023 17/19). Patients data were reviewed on the electronic charts of the Hospital Information System. Indications of PEG were cerebrovascular disease (CVD), Alzheimer's, motor neuron disease and trauma. In addition to standard demographic data such as age and gender of the patients, the following were recorded: PEG indications, length of hospital stays prior to the PEG procedure, presence of mortality, survival time, mechanical ventilator support, comorbidities, body mass index (BMI), hemoglobin, leukocyte, creatinine, albumin, and C-reactive protein (CRP) levels. Mortality data were obtained from the hospital records and the National Death Registry database. PEG was performed in the endoscopy unit or as a bedside procedure in the ICU if the transport of the patient was inappropriate. Enteral feeding was ceased 12 hours before the procedure. If the patient is not on antibiotics, 1 gram of intravenous cephazolin sodium was administered 4 hours before the procedure. The patient was monitored and nasal oxygen was delivered. Sedation was performed by a combination of midazolam and propofol. Pull technique was preferred for PEG placement in all patients.

All procedures were performed with a Pentax® fiber endoscope. A 20F PEG kit was used in all patients. Low-volume enteral feeding was initiated 24 hours after the procedure and increased gradually.

2.1. Statistical analysis

Data were analyzed with IBM SPSS® Statistics 26 software. Descriptive statistics were used for numerical variables (mean, standard derivation, minimum, maximum) and frequency distribution was used for categorical variables (number, percentage). Kaplan Meier and Cox regression analysis were used for the evaluation of the factors affecting survival. A p-value of <0.05 is regarded as statistically significant.

3. Results

The study group consisted of 137 patients with 71 females (51.8%) and 66 males (48.2%). Mean age of the patients was 78.75±12.08 years (range; 27-98 years). At the time of the PEG procedure, 82% of the patients were in the ICU and 18% were in the Palliative Care Unit. PEG indications were cerebrovascular disease in 60 (43.8%), Alzheimer's in 47 (34.3 %), motor neuron disease in 11 (8 %), and trauma in 19 (13.9%) (Table 1). Comorbidities were hypertension (HT) in 76.6%, atrial fibrillation (AF) in 45.3%, coronary artery disease (CAD) in 35.8%, diabetes mellitus (DM) in 35.8%, and chronic obstructive pulmonary disease (COPD) in 38,7%. Sixty-four patients (46.7%) were under mechanical ventilation support while the rest 73 (53.3%) were breathing spontaneously. Mean BMI was 25.45±3.63 (range; 18-32). In our study, the 1-month mortality rate was 16.7%, and the overall mortality rate at 38 months of follow-up was 51%. The higher mortality rate was found in patients with Alzheimer's and the lowest was in patients with motor neuron diseases (Table 2).

Kaplan-Meier analyses demonstrated no significant survival

Table 1

Demographics of the study group

		n	%
Age	mean±sd	78,75±12,08	
	(min-max)	(27-98)	
	≤80	62	45,3
	>80	75	54,7
Gender	• Female	71	51,8
	• Male	66	48,2
Length of hospital stay before PEG	mean±sd	29,52±18,35	
	(min-max)	(3-120)	
	• ≤30 day	81	59,1
	• >30 days	56	40,9
Respiration	• Spontaneous	73	53,3
	• Mechanical ventilation	64	46,7
Indications of PEG	• CVD	60	43,8
	• Alzheimer's	47	34,3
	• Motor neuron diseases	11	8,0
	• Trauma	19	13,9
BMI (kg/m2)	meant±sd (min-max)	25,45±3,63 (18-32)	
	• Normal	71	51,8
	• Overweight	47	34,3
	• Obese	19	13,9
HT		105	76,6
AF		62	45,3
CAD		49	35,8
DM		49	35,8
COPD		53	38,7
Hemoglobin (109/L)	meant±sd (min-max)	10,61±1,46, (7,4-13,4)	
Leukocyte (109/L)	meant±sd (min-max)	8,91±3,28 (4-16,7)	
Creatinin (mg/dL)	meant±sd (min-max)	1,15±0,98 (0,3-7)	
Albumin (g/L)	meant±sd (min-max)	27,46±3,51 (20,7-34,7)	
CRP (mg/dL)	meant±sd (min-max)	48,69±42,18 (3-181)	
Mortality	• 1-month mortality	23	16,7
	• Overall mortality	70	51

AF: Atrial fibrillation, BMI: Body mass index, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, CVD: Cerebrovascular disease, DM: Diyabetes mellitus, HT: Hypertension

Table 2

Mortality according to PEG indication

PEG indications (n=137)	1-month mortality n (%)	Overall mortality n (%)
CVD (n=60)	8 (13,3)	33 (55)
Alzheimer's (n=47)	13 (27,6)	27 (57,4)
Trauma (n=19)	2 (10,5)	9 (47,3)
Motor neuron diseases (n=11)	-	1 (9)

CVD: Cerebrovascular disease

difference with respect to age, gender, BMI and comorbidities (p>0.05). Survival was significantly higher in patients hospitalized shorter than 30 days before PEG placement than in patients hospitalized longer than 30 days (p=0,000). Survival was higher in patients with spontaneous breathing than the patients who were on mechanical ventilation support (p=0.032). Survival was significantly higher in patients with motor neuron diseases than the patients with Alzheimer's (p=0.036). Kaplan-Meier survival curves are given in Figure1-3.

Cox regression analyses revealed that the length of hospital stay before PEG placement and hemoglobin levels have a significant impact on survival. In patients with a length of hospital stay of more than 30 days before PEG placement, the risk of mortality was 2.502 times higher (1.557-4.022) compared to those with a length of hospital stay of 30 days or less, while a 1-unit decrease in hemoglobin levels was found to increase the risk of mortality by 1/0.808 = 1.238 times (1.055-1.453) (Table 3).

Figure 1

Kaplan-Meier Survival curve according to length of hospital stay before PEG placement (p=0,000)

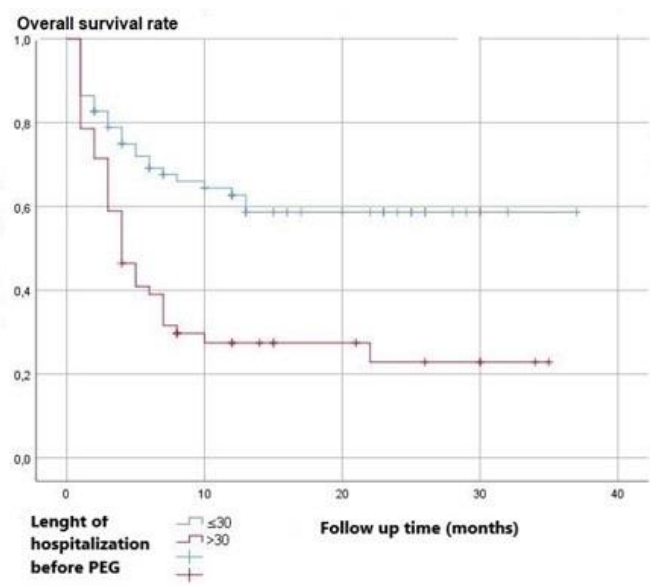

Figure 2

Kaplan-Meier Survival curve according to respiratory status (p=0,032)

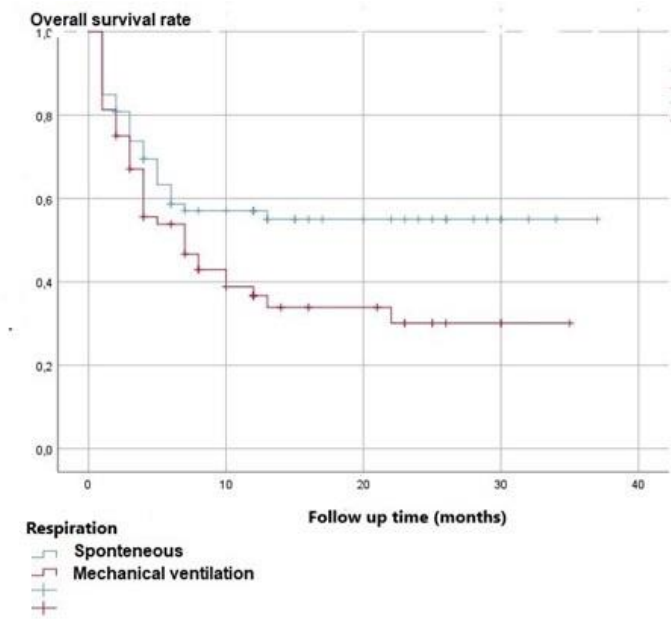

Figure 3

Kaplan-Meier Survival curve according to the indication for PEG tube. Survival was significantly higher in patients with motor neuron diseases than the patients with Alzheimer's (p=0,036)

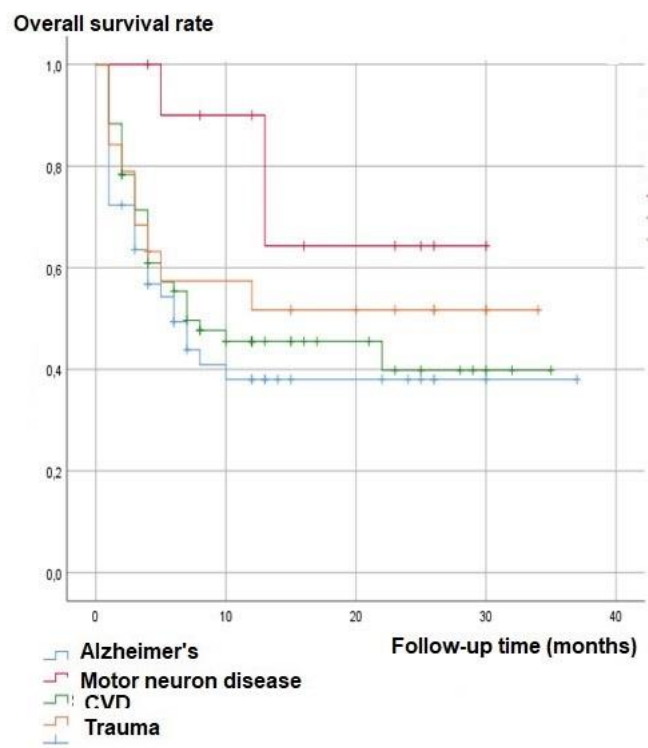

Table 3

Multivariate Cox regression analysis to determine independent prognostic factors affecting overall survival

	B	SE	Wald	p	HR	95,0% CI	
						Lower limit	Upper limit
Hospital stay before PEG (≤30 day vs >30 day)	0,917	0,242	14,347	0,000*	2,502	1,557	4,022
Hemoglobin (for 1 unit decrease)	-0,214	0,082	6,835	0,009*	0,808	0,688	0,948

CI: Confidence Interval, HR:Hazard ratio

4. Discussion

Nasogastric tube, nasojejunal tube, percutaneous fluoroscopic gastrostomy, surgical gastrostomy and PEG are enteral feeding options for patients who can not be fed by oral route despite patent gastrointestinal system[11]. Over time, PEG became a common endoscopic practice for enteral feeding purposes. PEG is considered to be superior to the other enteral feeding modalities due to lower aspiration risk[12,13]. Shorter procedure duration, lower cost and minimally invasive nature made rapid acceptance and widespread performance of the technique. However, it is not recommended to be performed in patients with a life expectancy of <30 days[14,15].

A study from England demonstrated a 60% reduction in 30-day mortality after the PEG procedure over 13 years. This result was attributed to improved patient selection and timing of the procedure[16]. In our study, the 1-month mortality rate was found to be 16.7%, and the overall mortality rate at 38 months of follow-up was 51%. Higher mortality rates in our study may be attributed to a high rate of patients with neurological disease as 43.8% had CVD and 34.3% had Alzheimer's in the study population. A study from Japan, which is also an aging country, reported reduced mortality rates by improving patient selection criteria, and that dementia is not an indication of PEG anymore[17].

The most common indications of PEG are dysphagia secondary to neurological conditions, head and neck malignancies and trauma[18,19]. A study from Türkiye indicated neurological diseases as the leading underlying cause leading to PEG placement with rates between 67-89.4%[20,21]. Consistent with the literature, neurological diseases were the most common indication of PEG in our patients, too (86.1%). The strong correlation between PEG placement and increased mortality in patients with malignancy has been demonstrated in many studies[22-24]. BMI was also reported as a risk factor for increased mortality[24]. The patients were divided into subgroups as normal, overweight and obese according to their BMI and no significant difference was observed among the groups for survival (p>0.05) in our study.

Procedure-related mortality is very low for PEG placement. Reported mortality is mostly related to primary or co-existing conditions rather than the procedure itself[25,26]. No mortality related with the PEG procedure itself is encountered in our study. Most patients who require nutritional support will need it for less than a month, and nasogastric tube feeding is the most commonly used method of tube feeding[27]. PEG tubes are widely used in long-term nutritional support. In our study, the hospital stay before PEG was 30 days or less in 81 (59.1%) patients. The risk of mortality in patients with a hospital stay of >30 days before PEG was found to be 2.5 times higher than in those with a hospital stay of ≤30 days (p=0.000).

The survival rate was found higher in patients who do not need ventilation support than the patients who need mechanical ventilation support (p=0.032). In patients requiring mechanical ventilator support, decreased survival rates may be attributed to the inherent disordered swallowing functions, complications associated with mechanical ventilation, and comorbidities leading to the need for ventilatory support. Subgroup analysis of PEG indications revealed that lowest mortality was in patients with motor neuron diseases and higher mortality was in patients with Alzheimer's which demonstrated a significant difference between the subgroups (p=0.036). Patients with Alzheimer's appear to have the worst prognosis. The indication for PEG is still under debate in patients with dementia (which includes Alzheimer's) to higher mortality rates after the procedure[28]. In our region, PEG is commonly performed in these patients due to the social pressure exerted by their families and relatives, possibly to soothe their conscience by ensuring they have provided the best medical care they can.

We did not find any significant impact of age, gender, BMI and comorbidities on the survival of the patients (p>0.05). Since the mean age of our patients is 78.75±12.08 years, we could not be able to compare young and elderly patients, and could only compare the elderly with the even older. A study involving younger patients with an average age of 65 demonstrated a significant relationship between advanced age and mortality[29]. Many previous studies demonstrated the relationship between co-existing diabetes and heart failure with mortality[24,30]. In our study, no significant difference was found between comorbidities and survival (p>0.05). Hemoglobin levels appear to have a significant impact on survival. One unit decrease in hemoglobin level is related with a 1.2-fold increase in mortality (p=0.009). Accordingly, our finding that lower hemoglobin levels are associated with worse outcomes is not surprising. This finding is also demonstrated by previous studies and low hemoglobin levels should be regarded as an indicator of serious underlying conditions[24].

The retrospective nature of the study increases the likelihood of bias in the interpretation of the results. Other limitations of our study is the small sample size and being conducted as a single-center study. Finally, the absence of patients with malignant diseases (which is a common indication of PEG) is another limitation of our study.

5. Conclusion

Hemoglobin levels, need for mechanical ventilation support and prolonged length of hospital stay before PEG procedure appear to have a significant impact on the survival. PEG tube placement should not be delayed when the need for long-term nutritional support is anticipated. Higher mortality in patients with Alzheimer's dictates that indication of PEG should be reevaluated in this subgroup. More extensive clinical studies are necessary to evaluate the role of PEG placement in individual subgroups of patients with different underlying conditions.

Statement of ethics

The study protocol was approved by the Samsun University KAEK-

2023 17/19.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author Contributions

BKY: Conceptualization and design of the study, data acquisition, data analysis, literature review, writing and editing of the manuscript, and critical review

MY: Conceptualization and design of the study, data analysis, literature review, writing and editing of the manuscript, and critical review

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Effectiveness of Propolis on Experimental Colitis Model in Rats

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Abstract

Aim: This study investigated the therapeutic potential of propolis in an experimental colitis model induced by acetic acid in female Wistar albino rats.

Methods: Thirty rats were divided into five groups: a control group and four experimental groups. Colitis was induced in the second, third, and fifth groups by rectal administration of 1 ml of 4% acetic acid. The third group received rectal propolis solution (50 mg/ml), while the fourth group was given only rectal propolis solution. The fifth group received 1 ml of olive oil rectally after the onset of colitis. Stool consistency and weight loss were monitored, and colon tissue samples were collected for microscopic and macroscopic evaluation. The levels of MDA, MPO, and caspase-3 in tissue, as well as TNF-α and IL-10 levels in blood samples, were examined.

Results: The group administered propolis showed a significant decrease in microscopic and macroscopic scores compared to the other experimental groups. The levels of MDA, MPO, and caspase-3 in the tissue, as well as TNF-α and IL-10 levels in blood samples, were significantly decreased in the propolis group compared to the other experimental groups. Weight loss and stool consistency also showed improvement in the propolis group compared to the other experimental groups.

Conclusions: Propolis may have therapeutic effects in experimental colitis induced by acetic acid. The decrease in oxidative damage and inflammation seen in the propolis group indicates that it may be a useful therapeutic agent for colitis treatment.

Keywords: *Acetic acids, colitis, ulcerative, rats, wistar, bee products, olive oil*

1. Introduction

The worldwide incidence and prevalence of inflammatory bowel diseases (IBD) is on the rise. [1] Although the etiology of IBD remains largely unknown, it is believed to result from an intricate interplay between genetic, environmental, microbial factors, and immune respons. [2, 3] The pathogenesis of IBD involves an uncontrolled immune system that interacts with the intestinal flora in genetically predisposed individuals, leading to an inflammatory response that primarily affects the digestive system. [4, 5] The main objective of medical intervention is to mitigate the extent of inflammation and maintain clinical remission.

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Various pharmacological agents, such as 5-aminosalicylate (5-ASA), corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, infliximab, and adalimumab, are employed for treating IBD. [6]

Rectal administration of acetic acid (4-10%) via a feeding catheter has been demonstrated to induce acute colitis in rats, mice, rabbits, and guinea pigs. [7] This type of colitis is characterized by necrosis and edema in the mucosal epithelium, with later stages exhibiting inflammation in both the mucosal and submucosal layers. Inflammatory cells and mediators lead to severe tissue damage. [8]

Propolis is a resinous substance produced by bees that combines extracts from plant buds and exudates with bee enzymes, pollen, and wax. [9]Its known properties include antiseptic, antimicrobial, anti-inflammatory, antitumor, immunomodulatory, and antioxidant effects. [10]

Experimental models of colitis play a critical role in preclinical research for developing effective treatments for inflammatory bowel diseases. Various therapeutic agents have been evaluated using diverse experimental colitis models.

The primary objective of this study is to investigate the efficacy of propolis in acetic acid-induced colitis in rats, as reported in the existing literature.

2. Materials and methods

This study was conducted in accordance with ethical guidelines and received approval from the ethics committee of Çukurova University Health Sciences Experimental Application and Research Center (SABIDAM), under protocol number TTU-2022-14631 and decision number 1 of the Animal Experiments Local Ethics Committee of Çukurova University Faculty of Medicine, dated 20.01.2022.

Thirty female Wistar Albino rats with an average weight of 200-260 grams were obtained from Çukurova University Health Sciences Experimental Application and Research Center and used in the experiments. The rats were housed individually in cages with a 12-hour light-dark cycle, and were provided with tap water and standard pellet feed at room temperature of approximately 22°C throughout the study.

2.1. Induction of colitis:

The experimental colitis was induced by using a 4% solution of acetic acid in this study. The administration of 1 cc of the acetic acid solution was performed by inserting the 6 F polyurethane catheter approximately 6-8 cm into the rectal route. To prevent the backflow of the administered substance, the rats were kept in the Trendelenburg position for 30 seconds. Subsequently, each rat was placed in its individual cage.

Groups:

Groups of rats were assigned as follows (Table 1):

Group 1: *Control group, no intervention, sacrificed after 120 hours.*

Group 2: *Acetic acid group, received 1 cc of 4% acetic acid intrarectally at the start of the experiment, sacrificed after 120 hours.*

Group 3: *Acetic acid + Propolis group, received 1 cc of 4% acetic acid intrarectally at the start of the experiment, then 1 cc of 5% propolis solution rectally at 4, 24, 48, and 72 hours, sacrificed after 120 hours.*

Group 4: *Propolis group, no intervention at the start of the experiment, then received 1 cc of propolis solution rectally at 4, 24, 48, and 72 hours, sacrificed after 120 hours.*

Group 5: *Acetic acid + Olive oil group, received 1 cc of 4% acetic acid intrarectally at the start of the experiment, then 1 cc of extra virgin olive oil rectally at 4, 24, 48, and 72 hours, sacrificed after 120 hours.*

Before starting the experiment, all rats were weighed, and their weights were recorded. The rats were placed in individual cages throughout the study.

The rats were sedated with a combination of 10 mg/kg xylazine hydrochloride (XYLAZIN BIO ®, 2%, Bioveta PLC Ivanovice na Hane-Czech Republic) and 90 mg/kg ketamine (Ketasol ®, Richter Pharma AG, Wels-Austria) given by intraperitoneal injection. Blood samples were taken by intracardiac puncture (2 cc) and collected in EDTA tubes. A laparotomy was performed with a Y-shaped incision to remove the left colon and rectum. The consistency of the stool sample from the rectum and left colon was checked, and the removed tissue was washed with +4 celcius degrees of saline solution. Half of the tissue was fixed in a formaldehyde solution in a sterile container, and the other half was placed in an Eppendorf tube and stored in liquid nitrogen solution. The Eppendorf tube was then stored in a freezer at -80 degrees Celsius.

2.2. Preparation of Propolis

The solution was prepared by taking 10 grams of pure and powdered propolis sample produced in the Black Sea Region and adding it to 200 milliliters of olive oil, as described by Krell (1996). The solution was gently heated at no more than 50 degrees Celsius for about 10 minutes in a hot water bath with constant stirring. After filtering, it was taken into amber-colored glass bottles and stored at +4 degrees in the refrigerator. [11]

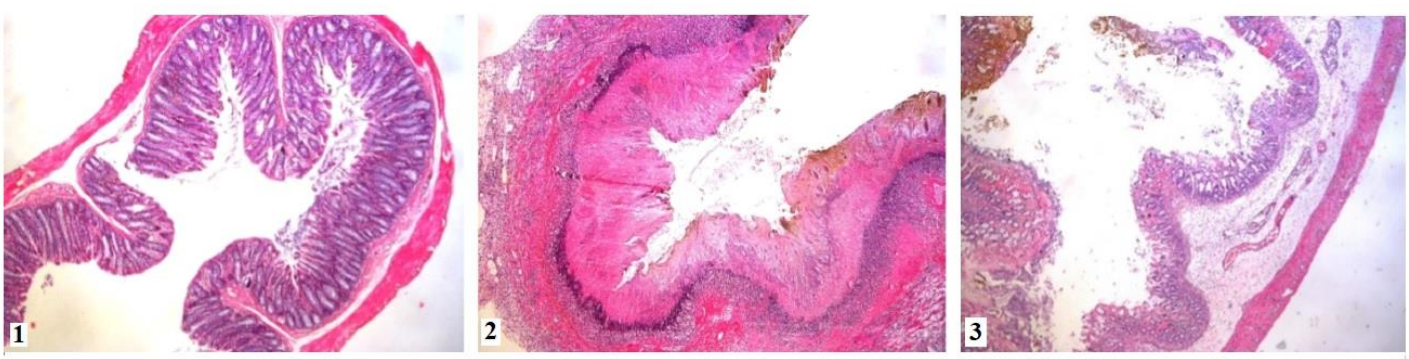
Before anesthesia was given to the rats in group 3 and group 4, they were administered 250mg/kg/day of the propolis solution rectally at the 4th, 24th, 48th, and 72nd hours.

2.3. Histopathological and Immunohistochemical Evaluation

The colon tissue was evaluated macroscopically and microscopically using scoring systems developed by Wallace and colleagues and Gaudio and colleagues, respectively. (Figures 1-5) Weight loss was assessed at the beginning and end of the study, and blood samples were collected for analysis of TNF-α, MPO, MDA, and IL-10 levels using ELISA kits and a SunRed ELISA microplate reader and washer. Absorbance was measured at 450 nm.

Figure 1, 2, 3

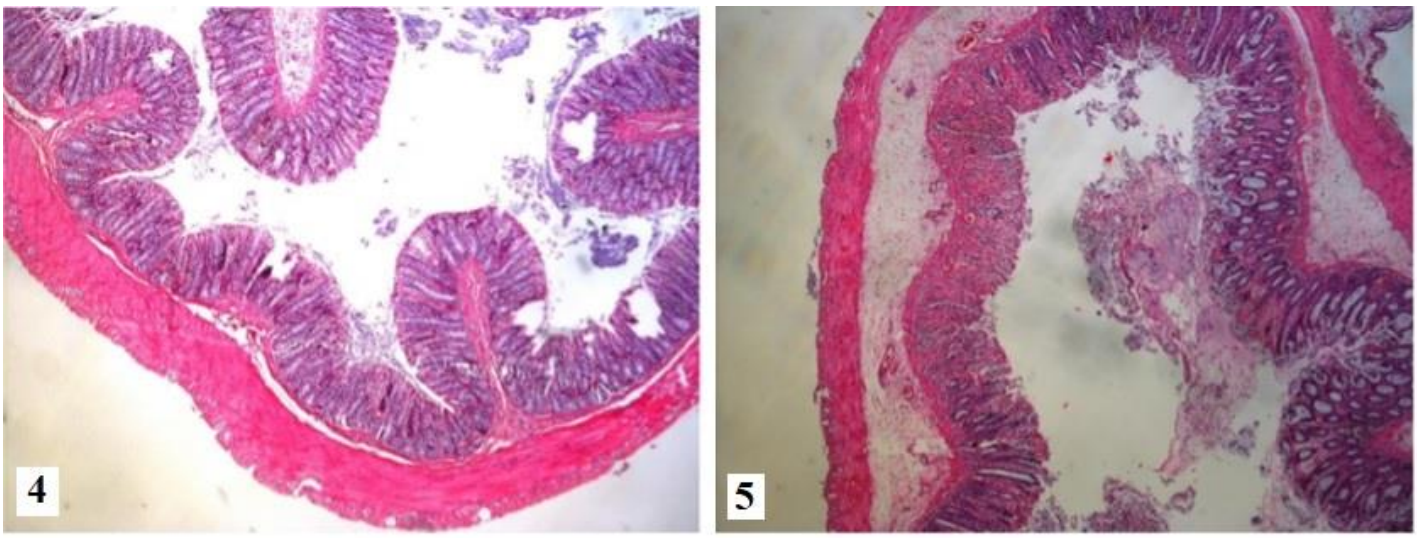
Microscopic view of control group, microscopic view of acetic acid group, microscopic view of acetic acid+propolis group



1. Microscopic view of control group [Control group rat colon histological image. A normal appearance is observed in the colonic mucosa. (40X magnification, H&E staining), 2. Microscopic view of acetic acid group [Acetic acid group rat colon histological image. Ulceration in the intestinal tissue, necrosis in the epithelium, acute and chronic inflammatory cells, submucosal edema, and fibrin deposition in the vessel walls are observed. (40X magnification, H&E staining)], 3. Microscopic view of acetic acid+propolis group [Mucosal damage is minimal, edema and inflammatory cells are observed in the submucosa (40X magnification, H&E staining)]

Figure 4, 5

Microscopic view of control group, microscopic view of acetic acid group, microscopic view of acetic acid+propolis group



4. Microscopic view of propolis group [Propolis group rat colon histological image. A normal appearance is observed in the colonic mucosa. (40X magnification, H&E staining)], 5. Microscopic view of acetic acid+olive oil group [Focal superficial ulceration, submucosal edema and mild inflammatory cells in the mucosa are observed. (40X magnification, H&E staining)]

2.4. Statistical analysis

Categorical data were presented as frequencies and percentages, while numerical data were expressed as mean and standard deviation (or median and range if necessary). The normal distribution assumption of the numerical data was checked by using the Shapiro Wilk test. One-Way Analysis of Variance was applied to compare the numerical data of more than two groups, provided that the assumptions were met. If the assumptions were not met, the Kruskal Wallis test was used instead. In cases where significant differences were detected among the groups, pairwise comparisons were performed using Bonferroni or Games & Howell tests, depending on the homogeneity of the variances. If the variances were not homogeneous, the Mann Whitney U test with Bonferroni correction was used. Statistical analysis was conducted using IBM SPSS Statistics Version 20.0, and the level of statistical significance was set at 0.05 for all tests.

3. Results

The study involved five groups, each consisting of six rats, with one rat in the acetic acid+olive oil group having died. The collected data, which included weight loss, stool consistency, macroscopic and microscopic scores, are displayed in Table 2.

Pairwise comparisons of weight loss scores revealed a significant difference between the acetic acid group and the propolis group ($p<0.05$), as well as between the propolis group and the acetic acid + olive oil group ($p<0.05$). Similarly, significant differences were found in stool consistency scores between the acetic acid group and the propolis and acetic acid + propolis groups ($p<0.05$), and between the propolis group and the acetic acid + olive oil group ($p<0.05$).

Table 1

Study groups

Groups	Protocol					
Group 1 (n=6)	-	-	-	-	-	Sacrification
Group 2 (n=6)	Acetic acid	-	-	-	-	Sacrification
Group 3 (n=6)	Acetid acid	Propolis	Propolis	Propolis	Propolis	Sacrification
Group 4 (n=6)	-	Propolis	Propolis	Propolis	Propolis	Sacrification
Group 5 (n=6)	Acetic acid	Olive Oil	Olive Oil	Olive Oil	Olive Oil	Sacrification
Hours	0	4	24	48	72	120

Microscopic scores differed significantly between the control group and the acetic acid group, and between the acetic acid and propolis groups ($p<0.05$). Furthermore, significant differences were detected between the acetic acid and acetic acid + olive oil groups in comparison to the control group, as well as between the acetic acid group and the propolis group ($p<0.05$) (Table 3).

Caspase-3 values differed significantly between the control group and the acetic acid group, between the acetic acid and propolis groups, and between the propolis group and the acetic acid + olive oil group ($p<0.005$). For MPO values, significant differences were found between the control group and the acetic acid, acetic acid + propolis, and acetic acid + olive oil groups ($p<0.05$).

Table 2

Weight Loss, stool consistency, macroscopic and microscopic scores by groups

Subjects	Groups	Weight Loss Score	Stool consistency	Macroscopic score	Microscopic score
1	CONTROL (K1)	0	1	0	0
2	CONTROL (K2)	0	1	0	0
3	CONTROL (K3)	1	1	0	1
4	CONTROL (K4)	0	1	0	0
5	CONTROL (K5)	0	1	0	1
6	CONTROL (K6)	0	2	0	1
7	ACETIC ACID (AA1)	4	3	6	18
8	ACETIC ACID (AA2)	3	3	7	17
9	ACETIC ACID (AA3)	3	3	6	18
10	ACETIC ACID (AA4)	2	2	7	18
11	ACETIC ACID (AA5)	3	3	6	20
12	ACETIC ACID (AA6)	4	3	5	17
13	ACETIC ACID + PROPOLIS (AA+PP1)	1	1	3	12
14	ACETIC ACID + PROPOLIS (AA+PP2)	1	2	2	8
15	ACETIC ACID + PROPOLIS (AA+PP3)	3	1	2	12
16	ACETIC ACID + PROPOLIS (AA+PP4)	3	1	3	12
17	ACETIC ACID + PROPOLIS (AA+PP5)	2	1	1	8
18	ACETIC ACID + PROPOLIS (AA+PP6)	2	2	3	10
19	PROPOLIS (PP1)	0	1	0	0
20	PROPOLIS (PP2)	0	1	0	0
21	PROPOLIS (PP3)	0	1	1	0
22	PROPOLIS (PP4)	1	1	0	2
23	PROPOLIS (PP5)	0	1	0	1
24	PROPOLIS (PP6)	1	2	0	0
25	ACETIC ACID + OLIVE OIL (AA+OO1)	3	2	5	14
26	ACETIC ACID + OLIVE OIL (AA+OO2)	2	2	4	12
27	ACETIC ACID + OLIVE OIL (AA+OO3)	2	1	2	8
28	ACETIC ACID + OLIVE OIL (AA+OO4)	3	2	4	14
29	ACETIC ACID + OLIVE OIL (AA+OO5)	4	3	3	13

A significant difference was also observed between the acetic acid + propolis group and the propolis group ($p<0.05$). Comparisons of TNF-α values between groups revealed significant differences between the control group and the acetic acid, acetic acid + propolis, propolis, and acetic acid + olive oil groups ($p<0.05$), as well as between the acetic acid + propolis group and the propolis group ($p<0.05$) (Table 3).

4. Discussion

The primary aim of therapeutic interventions in experimental models of colitis is to mitigate inflammation and minimize tissue necrosis. To evaluate the severity of inflammation and tissue damage, various parameters have been employed, including macroscopic and microscopic examinations, stool analyses, and more quantitative and objective biochemical and immunohistochemical measurements. Numerous bioactive compounds have been investigated for their protective effects against colitis via oral and rectal administration. The latter is considered safer due to the reduced toxicity and side effects of the drug. Oruc et al. (2008) investigated the potential efficacy of leflunomide in treating experimental colitis induced by acetic acid in rats. Their study demonstrated that intragastric administration of leflunomide significantly decreased the severity of colitis by reducing MDA levels. [12]

Propolis has been the subject of many experimental investigations exploring its positive effects. A systematic review conducted by Ruiz-Hurtado et al. (2021) examined the effects of orally administered propolis on gastric ulcer induced by non-steroidal anti-inflammatory drugs (NSAIDs) in the gastrointestinal system. The review analyzed studies conducted between 2000-2021 and demonstrated that propolis can be effective in treating NSAID-induced gastric ulcers. This effect is attributed to its antioxidative, anti-inflammatory, and cytoprotective properties, which inhibit gastric acid secretion

and pro-inflammatory cytokine release. [13]

Table 3

Statistical analysis of clinical, biochemical and immunohistochemical parameters

	Groups					p
	Control	Acetic acid	Acetic acid + propolis	Propolis	Acetic acid + olive oil	
Weight Loss Score	0.0(0.0-1.0)[a,d]	3.0(2.0-4.0)[c]	2.0(1.0-3.0)	0.0(0.0-1.0)[d]	3.0(2.0-4.0)	<0.001
Stool Consistency Score	1.0(1.0-2.0)[a]	3.0(2.0-3.0)[b,c]	1.0(1.0-2.0)	1.0(1.0-2.0)	2.0(1.0-3.0)	0.001
Macroscopic Score	0.0(0.0-0.0)[a]	6.0(5.0-7.0)[c]	2.5(1.0-3.0)	0.0(0.0-1.0)	4.0(2.0-5.0)	<0.001
Microscopic Score	0.5(0.0-1.0)[a]	18.0(17.0-20.0)[c]	11.0(8.0-12.0)	0.0(0.0-2.0)	13.0(8.0-14.0)	<0.001
Weight change	0.0(-6.0;0.0)[a,d]	-42.0(-52.0-20.0)[c]	-17.0(-40.0-4.0)	-1.0(-4.0;0.0)	-28.0(-42.0-16.0)	<0.001
Weight loss(%)	0.0(0.0;2.0)[a,d]	17.0(7.0;20.0)[c]	7.0(1.0;17.0)	0.0(0.0;1.0)	11.0(6.0;20.0)	<0.001
Caspase-3	7.5(5.0;20.0)[a]	45.0(40.0;60.0)[c]	20.0(10.0;30.0)	5.0(5.0;10.0)[d]	40.0(20.0;40.0)	<0.001
MPO	214.2±8.7[a,b,d]	271.0±11.3[b,c]	239.8±6.7[c]	212.4±21.2[d]	248.3±6.1	<0.001
MDA	24.9±3.1[a,b,d]	43.9±2.3[b,c,d]	31.4±1.9[c]	25.3±3.2[d]	35.0±3.0	<0.001
IL_10	229.5±14.8	198.6±73.0	197.0±46.3	189.8±26.8	183.6±35.1	0.465
TNF-α	177.1±16.3[a,b,c,d]	279.4±13.3[b,c,d]	233.8±13.1[c]	207.4±5.0	237.4±19.7	<0.001

Data are summarized as mean±standard deviation or median(min;max). ap<0.05 compared to acetic acid, bp<0.05 compared to acetic acid+propolis, cp<0.05 compared to propolis, dp<0.05 compared to acetic acid+olive oil.

Propolis has been suggested to possess anti-inflammatory properties in the context of colitis, possibly mediated through its impact on the gut microbiota. Krocko et al.(2012) found that the addition of propolis and bee pollen to chicken feed resulted in a decrease in the colonization of enterobacteria in chicken crops, but had no effect on lactobacilli. [14] Similarly, Wang et al. (2018) demonstrated that propolis administration reduced colitis severity, colonic apoptosis, and significantly reduced the colonization of bacterioides in the intestines. [15]

In experimental colitis models, propolis has shown a general anti-inflammatory and cytoprotective effect. One study by Khan et al. (2018) using a DSS-induced colitis model suggested that intraperitoneal administration of the active component of propolis, caffeic acid phenyl ester (CAPE), has a protective effect against colitis. However, the study also found that the level of anti-inflammatory cytokine IL-10 was lower in the CAPE-treated group compared to the colitis group, which was attributed to the suppressive effect of CAPE on IL-10. [16] In our study, we observed weight loss in the acetic acid group compared to the control group, and a significant difference in weight loss between the acetic acid group and the acetic acid+propolis group. Additionally, MPO and TNF-α values were significantly higher in the acetic acid group than in the acetic acid+propolis group, which supports the anti-inflammatory activity of propolis. However, we did not observe a statistically significant difference in IL-10 values between the acetic acid group and the acetic acid+propolis group.

Gonçalves et al. (2013) conducted a study on a TNBS-induced colitis model using rectal propolis and mesalazine in 50 rats. They evaluated colitis activity by examining stool consistency score, macroscopic score, microscopic score, and MPO activity using histological studies. In their study, colitis was induced with 20 mg of TNBS, and treatment was initiated 48 hours after colitis was induced using 0.8 ml of 8% propolis extract or mesalazine solution for 5 or 12 days. [17] The study showed that delaying the initiation of treatment led to the development of inflammation. The results of the study showed that there was no significant difference between the acetic acid+propolis group and the acetic acid group in terms of stool score, macroscopic score, microscopic score, and MPO values. In our study, on the other hand, we found a significant difference between the two groups in terms of stool consistency score and MPO, but no significant difference was found in microscopic and macroscopic scores. The difference in the results of the two studies may be due to the late onset of treatment in the other study.

According to a study conducted by Aslan et al. (2007), a distal colitis model induced with acetic acid was used to divide 40 mice into 5 groups. The control group constituted the first group, while the second group comprised the colitis group. The third and fourth groups consisted of the colitis + example enema group and the colitis + intragastric propolis group, respectively. The fifth group was designated as the colitis + mesalamine enema + intragastric propolis group. After sacrifice, the 8 cm distal colon was examined both histopathologically and biochemically. Histologically, less tissue damage was observed in the colitis + propolis group compared to both the colitis + mesalamine group and the colitis group. In the biochemical analysis, the colitis group exhibited significantly higher MDA values than the colitis + propolis group, although no significant difference was observed in the MPO values. [18] Our study observed statistically significant differences in both MDA and MPO values be-

tween the acetic acid and acetic acid + propolis groups. This discrepancy between the two studies may be attributed to the different route of propolis administration.

Activation of apoptotic pathways indicated by up-regulation of caspase-3 is considered a marker of colitis severity. [19, 20] Murad et al. (2022) investigated the effects of active olmesartan medoxomil on a TNBS-induced colitis rat model and assessed colitis activity score, MPO, TNF-α, IL-6, MDA, GSH, as well as E-cadherin, caspase 3, and matrix metalloproteinase-9 (MMP-9) expression in colon segments using immunohistochemistry. Olmesartan treatment led to significantly reduced MPO activity, TNF-α, and MDA levels compared to the colitis group. [21] In our study, we found that MPO activity, TNF-α activity, and MDA levels were significantly lower in the acetic acid+propolis group compared to the acetic acid group. However, while olmesartan treatment resulted in down-regulation of caspase-3 levels and prevented apoptotic pathway activation, the acetic acid + propolis group showed lower caspase-3 levels compared to the acetic acid group, with no significant difference between the two groups. This suggests that propolis' anti-apoptotic effect may be more limited than its anti-inflammatory effect.

There were significant differences between the acetic acid group and the control group in terms of various clinical, biochemical and immunohistochemical parameters including weight loss, stool score, macroscopic and microscopic scores, weight change and percent weight loss. These differences indicated the development of colitis in the acetic acid group, as demonstrated by elevated levels of Caspase-3, MPO, MDA and TNF-α.

In comparison, the propolis group showed no significant differences in weight loss, stool score, macroscopic and microscopic scores, weight change and percent weight loss compared to the control group. Additionally, there were no significant differences in Caspase-3, MPO, MDA and IL-10 levels. However, TNF-α levels were significantly higher in the propolis group compared to the control group, although no clinical or microscopic signs of colitis were observed. Nonetheless, TNF-α levels were lower in the propolis group compared to all colitis groups. Moreover, the weight change in the propolis group was similar to that of the control group.

The primary objective of our study was to investigate the differences between the acetic acid + propolis group and the acetic acid group. The stool score of the acetic acid group was significantly higher than that of the acetic acid + propolis group. Although not statistically significant, the other clinical parameters, such as weight loss score, macroscopic and microscopic scores, weight change, and percent weight loss, had lower median, minimum, and maximum values in the acetic acid + propolis group, providing evidence for the protective effect of propolis against colitis. The lower levels of pro-inflammatory cytokines TNF-α and tissue destruction products MPO and MDA in the acetic acid+propolis group compared to the acetic acid group indicate the cytoprotective activity of propolis in colitis at the biochemical level.

The limitations of our study include the lack of evaluation of the antibacterial activity of propolis and the difficulty in determining the optimal dose of rectal propolis. Moreover, the absence of a group administered only olive oil limits the evaluation of the effectiveness of olive oil. Additionally, we could not compare the effectiveness of oral and rectal propolis as there was no group given oral propolis.

5. Conclusion

Propolis is a well-known substance with anti-inflammatory properties and its low cost and ease of production make it an advantageous option compared to other drugs. Our study shows that propolis, which has previously been shown to have positive effects on colitis when taken orally, can also be used rectally for the treatment of colitis. The rectal route is preferred in colitis treatment due to the reduced risk of systemic side effects. While propolis and olive oil have similar anti-inflammatory activity on a biochemical level, our study suggests that propolis is superior to olive oil in terms of its clinical effectiveness. The literature contains numerous publications demonstrating the anti-inflammatory and antibacterial effects of propolis, as well as its protective effect against colitis, and our study supports these findings.

Statement of ethics

The study protocol was approved by the Cukurova University TTU-2022-14631

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Predicting Acute Pancreatitis Severity: A Comparative Analysis of Computed Tomography Severity Index, Including Fat and Muscle Parameters

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Abstract

Aim: The aim of this study was to investigate whether computed tomography-measured intra-abdominal fat and muscle parameters could improve the accuracy of acute pancreatitis severity assessment using the computed tomography severity index.

Methods: This retrospective study included clinical and imaging parameters of 87 patients with acute pancreatitis. Patients were assessed by the computed tomography severity index. Asan J-Morphometry (Seoul, Korea), an ImageJ-based software (NIH, USA), was used to quantify abdominal muscle and fat areas. Total fat area, superficial fat area, visceral fat area, total muscle area and total muscle-fat area were calculated. The severity of acute pancreatitis was determined according to the revised Atlanta classification. Interreader agreement assessments, univariate and multivariate analyses were performed.

Results: No significant differences were found in intra-abdominal fat and muscle parameters between groups with or without systemic or local complications ($p > 0.05$). When the patients were categorized as mild and severe disease based on computed tomography severity index score, no significant differences were found in fat and muscle parameters ($p > 0.05$). Surgery, systemic complications, and a high total computed tomography severity index score significantly increased the risk of local complications, with odds ratios of 0.001, 141.9, and 2.42, respectively. The intraclass correlation coefficients (ICC) were ≥ 0.90 between the readers.

Conclusions: In this study, our study suggested that computed tomography -measured fat and muscle parameters did not significantly improve the accuracy of computed tomography severity index in predicting severity of acute pancreatitis.

Keywords: *Acute pancreatitis, Atlanta classification, computed tomography, computed tomography severity index, disease severity, fat, muscle*

1. Introduction

Acute pancreatitis (AP) is a prevalent gastrointestinal condition with potentially life-threatening complications, affecting up to 20% of patients.[1-3] Though widely used, the Balthazar score alone struggles to predict organ failure or mortality. For more accurate diagnoses, computed-tomography (CT) severity index combines Balthazar grading with pancreatic necrosis with scores above 5 linked to higher mortality and longer hospital stays.[4-7] Early and accurate assessment of severity is crucial to identify those at risk and prevent adverse outcomes, as morbidity and mortality remain high for severe cases.[3] Previous research suggests promising roles for visceral fat surface area and peritoneal cavity circumference in early prediction of severity and mortality.[8,9] This study investigates the potential of CT-derived measurements of intraabdominal fat and muscle indices, alongside the established Balthazar score, to improve the accuracy of AP severity assessment.

Our objective is to refine the assessment of AP severity by exploring the combined predictive power of CT-measured intraabdominal fat and muscle parameters with the Balthazar score. This novel approach has the potential to enhance patient management strategies and optimize risk stratification in this critical condition.

2. Materials and methods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Adana City

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Training and Research Hospital Clinical Research Ethics Committee, (approval date:17.11.2022, project number:2246). Patients with AP referred/admitted to the department of general surgery from January 2018 to January 2021 were searched and among these cases, those who had a computed tomography scan at the time of diagnosis of AP were included in the study.

All CT scans were performed on a 128-slice Philips Ingenuity scanner (Eindhoven, Netherlands) at portal venous phase. All images were anonymized and independently reviewed by two physician specialists: a radiologist and a general surgeon specializing in gastrointestinal surgery. Both reviewers were blinded to patients' clinical data.

All CT scans were analyzed using Asan J-Morphometry software (Seoul, Korea), dedicated for abdominal muscle and fat area measurements based on ImageJ (NIH, USA).

2.1. Muscle and Fat Measurements

Following Schweitzer et al.[10], measurements were done on a single axial slice at the level of the inferior endplate of the third lumbar vertebra (L3). According to the different Hounsfield units, densities of different tissue types, the software automatically calculates the skeletal muscle area (–29 to +150), abdominal fat area (–50 to –150), and subcutaneous fat area (–190 to –30). The software automatically segmented and allowed manual adjustments for visceral fat area (within total abdominal muscle area), total muscle area (including abdominal wall, psoas, and paraspinal muscles)

Calculated parameters included: total fat area (TFA), Superficial fat area (SFA) = TFA - visceral fat area (VFA), Total muscle area (MA), Total muscle-fat area (MFA)

Balthazar score was assessed as follows: normal pancreas: 0**,** pancreas enlargement: 1**,** pancreatic/peripancreatic inflammation: 2, single ill-defined fluid collection: 3**,** two or more poorly defined fluid collections: 4.

Pancreatic necrosis score was categorized as follows: none: 0, **≤** 30%: 2, 30-50%: 4, 50%: 6

The computed tomography severity index was defined as the sum of Balthazar and necrosis scores (maximum 10).

Clinical severity was assessed by the Atlanta classification. Additionally, demographic data (age, gender) and clinical information were collected, including: etiological factors contributing to pancreatitis, mortality rates, occurrence of local and systemic complications, time to initiate feeding, duration of hospital stay, incidence of surgical or interventional procedures.

2.2. Statistical analysis

IBM SPSS software was used to analyze data. Categorical data were summarized with frequencies and percentages, while continuous data were summarized with various statistics like mean, standard deviation, and median. Statistical tests (chi-square, Fisher's exact, Mann-Whitney U) were used to compare variables based on their distribution and sample size. Significance was defined as $p < 0.05$.

Univariate models and Receiver Operating Characteristic (ROC) curve analysis were used to assess individual associations and the performance of selected variables and CT severity index in predicting outcomes. ROC analysis identified the best cutoff value for these variables, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

The reader agreement was assessed with intraclass correlation coefficient (ICC) ($r \geq 0.90$ excellent, 0.70-0.90 good, 0.50-0.70 fair, 0.30-0.50 weak, <0.30 poor).

3. Results

Initially eighty-eight patients diagnosed with AP admitted to our department were considered. One patient with cachexia due to rectal carcinoma was excluded. Therefore, our analysis included 87 participants. The mean age of the patients was 51.6±18.9 years, and of those 48 (55.2%) were male. The most frequent contributors to pancreatitis were gallstones (60.9%), followed by hyperlipidemia (20.8%).

According to the Atlanta classification, disease severity was classified as moderate in 36 patients (41.4%), mild in 32 patients (36.8%), and severe in 19 patients (21. 8%).We categorized mild cases as non-severe and combined moderate and severe cases as severe for statistical analysis.

Local complications were detected in 28 cases (32.2%)and systemic complications were developed in 36 cases (41.4%). Mortality rate was 2.3% (n=2). Additionally, 16.1% of the patients (n=14) underwent surgical or interventional procedures. Total CT severity index score was 2,86±1,8 (ranging from 0 to 9). The detailed demographic and clinical data are presented in Table 1.

Inter-reader agreement was excellent for all CT parameters, with ICCs ranging from 0.95 to 0.99. When a cutoff of 4 or higher was considered for the total CT severity index score, the diagnostic performance was as follows: sensitivity 81.25% (95% CI: 63.6-92.8), specificity 49.09% (95% CI: 35.4-62.9), positive predictive value (PPV) 51% (95% CI: 42.7-59.2), negative predictive value (NPV) 90% (95% CI: 74.8-96.5), and area under the curve (AUC) 0.721 (95% CI: 0.615-0.812) ($p < 0.001$).

When cases were grouped into mild and severe disease based on the total CT severity index score, no statistically significant differences were observed among the groups in terms of TFA, SFA, MA, and MFA (with p-values of 0.307, 0.15, 0.49, and 0.13, respectively). In patients with severe Atlanta findings, a higher rate of surgical interventions was observed ($p < 0.001$).

Table 1

The clinical parameters of the study population

	Number (n)	percentage (%)
Atlanta		
• Mild	32	36.8
• moderate	36	41.4
• Severe	19	21.8
Surgical intervention		
• Yes	14	16.1
• No	73	83.9
Distribution of the Interventions	14	16.1
• abscess drainage	2	14.2
• debridement	2	14.2
• cystogastrostomy	1	7.1
• cholecystectomy	2	14.2
• percutaneous drainage	7	50.3
Mortality	2	2.3
Local complications	28	32.2
• Wall of necrosis	4	4.6
• Abscess, fluid, pseudocyst	21	24.1
• Wound related complications	3	3.5
Systemic complications	36	41.4
• sepsis	32	36.8
• ARDS	10	11.5
• acute renal failure	4	4.6
• cholangitis	1	1.1

Table 2

Univariate analysis. Comparison of variables between patients with Severe and Non-severe acute pancreatitis

	Atlanta non-severe (n=32)	Atlanta severe (n=55)	p[b]
	mean±SD	mean±SD	
Age	53.1±19.8	50.7±18.6	0.517
Total CT severity index score	2.13±1.5	3.29±1.8	<0.001**
Time to feeding	2.19±1.8	6.07±6.6	<0.001**
Hospitalization	5.31±3.6	14.9±13.2	<0.001**
TFA	401.6±209.6	566.6±825.3	0.686
SFA	206.4±117.5	194.8±110.9	0.745
VFA	162.3±101.5	191.1±112.7	0.221
MA	113.6±34.1	123.2±43.9	0.365
MFA	34.3±16.8	33.3±13.5	0.905

** p<0.05, **p<0.001, a: chi-square - Fisher exact test, b: Mann Whitney U test, TFA: Total fat area, SFA:superficial fat area,VFA: visceral fat area, MA: total muscle area, MFA: total muscle-fat area*

Univariate analyses were performed, including parameters such as patients' gender, surgery, sepsis, systemic complications, age total CT severity index score, time to feeding, hospitalization, CT-measured fat and muscle parameters. According to the univariate analysis, results based on the presence of local complications, it was determined that surgery, sepsis, systemic complications, age, total CT severity index score, time to feeding, and hospitalization time parameters were significant ($p < 0.05$). Univariate analyses are presented in Table 2 and Table 3.

The parameters found to be significant in the univariate analysis were included in the multivariate analysis. Surgery, systemic complications, and a high total CT severity index score significantly increased the risk of local complications, with odds ratios of 0.001, 141.9, and 2.42, respectively.

Table 3

Univariate analysis. Comparison of variables between patients with Severe and Non-severe acute pancreatitis

	Atlanta non-severe (n=32) n(%)	Atlanta severe (n=55) n(%)	p[a]
Sex			
• Male	15 (46.9)	33 (60)	0.235
• Female	17 (53.1)	22 (40)	
Surgery			
• Yes	2 (6.3)	12 (21.8)	0.043*
• No	30 (93,8)	43 (78.2)	
Mortality	-	2 (3.6)	0.275
Local complication	1 (3.1)	27 (50)	<0.001**
• wall of necrosis	-	4 (7.3)	0.118
• abscess-fluid-pseudocyst	1 (3.1)	20 (36.4)	<0.001**
• wound related complications	-	3 (5.5)	0.179
Systemic complication	2 (6.3)	34 (61.8)	<0.001**
• Sepsis	1 (3.1)	31 (56.4)	<0.001**
• ARDS	-	10 (18.2)	0.010*
• Acute renal failure	-	4 (7.3)	0.118
• cholangitis	1 (3.1)	-	0.187

** p<0.05, **p<0.001, a: chi-square - Fisher exact test, b: Mann Whitney U test, ARDS: acute respiratory distress syndrome*

No significant differences were found in intra-abdominal fat and muscle parameters between groups with or without systemic or local complications ($p > 0.05$). When the patients were categorized as mild and severe disease based on computed tomography severity index score, no significant differences were found in fat and muscle parameters ($p > 0.05$).

4. Discussion

Although there are several studies evaluating the impact of body composition including fat and muscle distributions on outcomes of AP, the findings are still controversial. Our study demonstrated that fat and muscle parameters measured by CT did not differ among the groups with severe or mild disease based on either Atlanta classification or CT severity index. Furthermore, adding CT-measured parameters did not appear to improve the predictive power of the CT severity index score in AP. As expected, our study also found that surgical and interventional procedures were more prevalent in cases with more severe Atlanta findings. The presence of surgery, systemic complications, or a high CT severity index score appeared as risk factors for local complications. Consistent with our expectations, gallstones were identified as the most significant etiological factor. Interestingly, a high level of agreement was observed between measurements performed by radiologists and gastroenterology surgeons.

Gupta et al.[11] proposed a new fat modified scoring system for pancreatitis using automated software. It categorizes patients based on fat levels and traditional methods in predicting severity. Notably, in that study total to visceral fat ratio based version showed the best accuracy. They suggested that their fat modified scoring system especially the total to visceral fat ratio version, could be a valuable tool for improved pancreatitis diagnosis. In our study we did not show a significant difference in superficial, visceral or total fat area between severe and non-severe AP patients. Acute pancreatitis is a complex and highly inflammatory systemic condition. The factors including genetics, age, gender, diet, physical activity, hormonal imbalances, and certain medical conditions may affect the abdominal fat and muscle area may vary. These factors could potentially influence our study results. Individual differences and specific conditions also might play a role in disease severity and fat-muscle distribution. Pre-admission co-morbidities also varied between studies.

In a recent study by Lin et al.[12], the mortality group had a lower third lumbar skeletal muscle index compared to the survival group among AP patients and the skeletal muscle index showed a negative correlation with CT severity index scores. They proposed that diagnosing muscle depletion using third lumbar skeletal muscle index was a valuable radiological parameter for predicting in-hospital severity and short-term prognosis in patients with AP. In our study population mortality rates were too small and we were unable to compare the survival and mortality groups. Since fat and muscle parameters did not vary between severe and non-severe groups in our study, we could not determine a cut-off value. Therefore, it was not possible to add CT-measured fat and muscle parameters to the Balthazar score and analyze them.

Wang S. et al.[13] measured body composition parameters on a single slice at L2-3 of the unenhanced CT scans. They assessed the intermuscular adipose tissue, visceral adipose tissue, skeletal muscle area and skeletal muscle density. The intermuscular adipose tissue and visceral adipose tissue were higher in the severe AP group than in the moderately severe group, but were not associated with outcomes. The proposed that low skeletal muscle density was associated with poor outcomes in patients with severe and moderately severe AP. In our study, as in the study of Wang et al, no difference was

detected in the skeletal muscle area between cases with severe and non-severe acute pancreatitis. Additionally, Fu et al.[14] showed that rates of local complications, splenic vein thrombosis, and organ failure were increased in AP patients with lower psoas muscle area. Psoas muscle area showed good ability to predict splenic vein thrombosis in women. In contrast to this study, our study found no significant difference in CT-measured muscle parameters between patients with and without local complications. In our study, total CT-severity index score significantly increased the risk of local complications, with an odds ratio of 2.42, unlike other CT-measured fat and muscle parameters

Dawra et al.[15] notably found a strong correlation between CT and Dual-energy X-ray absorptiometry (DXA)derived abdominal fat measurements in AP patients, suggesting both techniques are valuable for assessing fat levels and their potential links to AP severity. Additionally, they found associations between both CT and DXA fat measurements and AP severity, highlighting the potential of non-invasive DXA as an alternative to CT for abdominal fat assessment in AP. However, it's worth noting that their study population was significantly younger than ours (38.2 years vs. 51.6years), and age can influence the fat-to-muscle ratio, potentially explaining some of the discrepancies between the studies.

The literature suggests obesity as an important prognostic factor, with body mass index exceeding 30 kg/m^2 increasing mortality and severe disease progression.[16-18] However, Higaki et al.[19] demonstrated that abdominal visceral obesity (assessed by umbilical-level visceral fat area) did not significantly impact mortality prediction compared to age and a prognostic factor score in severe AP patients in the Japanese population. Similarly, to their study, we found no correlation between CT-measured fat and muscle parameters and patient prognosis. Notably, survival times did not significantly differ between severe AP patients with and without visceral fat area exceeding 167 cm^2. [19]

4.1. Limitation

Our study has a few limitations including relatively small sample size and retrospective design.

The strength of our study is the double-blinded nature of the CT measurements. Analyzing the inter-reader correlation provided valuable information about measurement consistency.

5. Conclusion

No significant differences were found in CT measurements between groups with or without systemic or local complications, or between groups categorized as mild and severe based on total CT severity index scores. This study's findings suggest that CT-measured abdominal fat and muscle parameters do not significantly enhance the accuracy of the CT severity index in predicting local and/or systemic complications in AP patients.

Statement of ethics

This retrospective cohort study was approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee, (The project number is 2246, approval date:17.11.2022).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

GO: Conceptualization, Project administration, Data curation, Formal Analysis, Writing – original draft, BCP: Data curation, Formal Analysis, Writing –review & editing, AS &AS: Data curation, Formal Analysis, Writing –review & editing

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Correlation Between Urethral Length and Urethral Stricture After Transurethral Resection of Prostate

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Abstract

Aim: To show the effects of urethral length, and surgical or patient related parameters on urethral strictures after Transurethral Prostate Resection (TURP).

Methods: The study included 127 patients who underwent TURP for benign prostate hyperplasia (BPH) unresponsive to medical treatment in our clinic between May 2019 and February 2020. The patients were separated into two subgroups as those who underwent second surgery because of urethral stricture and those who did not. These two groups were compared in respect of age, height, weight, total prostate specific antigen, fall in hemoglobin values, increase in urine peak flow rate, decrease in the post-micturition residual volume, prostate volume, operating time, tissue amounts, resection rate, and urethral length.

Results: Urethral stricture was determined in 13.4% of the patients. A statistically significant difference was determined between the two groups in respect of age and urethral length ($p<0.05$). At the postoperative 6-week follow-up, urine peak flow rates were seen to be statistically significantly lower in the stricture group ($p<0.05$).

Conclusions: Together with an increase in urethral length there could be an increased risk of damage to the urethral mucosa, and it should be kept in mind that this could contribute to the development of urethral stricture.

Keywords: *Benign prostate hyperplasia; urethral stricture; urethral length; transurethral prostate resection*

1. Introduction

Transurethral resection of the prostate (TURP) is the gold standard surgical treatment method for prostates of moderate volume (30-80 cc) and lower urinary system symptoms that have formed due to benign prostate hyperplasia (BPH). Although the high success rates of TURP have been proven with symptom scores, urine flow rates, and other functional parameters, this surgery has been associated with significant morbidities such as perioperative and postoperative bleeding, prolonged length of stay in hospital, recurrent urethral strictures, urinary incontinence, retrograde ejaculation, and erectile dysfunction.[1] Urethral stricture, which is one of the oldest and most difficult to treat diseases in urology, is known to be caused by scar formation in the urethral subepithelial tissue. Urethral strictures are seen in the late period in 2.7% of endourological interventions.[2] It has been reported in the range of 2.2%-9.8% following TURP.[3] Stricture is seen within the first 6 months in most patients.

The monopolar energy used in the traditional method has been replaced by bipolar energy based on a new radiofrequency system. Bipolar energy is a part of the electromagnetic spectrum, and requires completion of the bipolar current in the electrode used. Different techniques are used for this, and the current emerging from the end of the electrode can be converted to a second parallel electrode.[4] Isotonic physiological saline is used as fluid. In surgeries where this method is used, there has been shown to be a lower risk of urethral stricture as the electric current does not pass through the urethra.[5]

The etiology of urethral strictures is examined in four main groups of idiopathic, iatrogenic, inflammatory, and traumatic. Idiopathic and iatrogenic strictures are the most common strictures seen at the rate of 33%, followed by traumatic causes at 19% and inflammatory causes at 15%[6]. The leading iatrogenic cause, at the rate of 41%, is transurethral resections (TUR). Other causes include prolonged urethral catheterization, hypospadias repair, and prostatectomy procedures (open, laparoscopic or robotic prostatectomy).[7]

Patients with urethral stricture after prostate surgery usually present with weak urine flow, urinary infection, and sometimes acute retention.[5] Just as the length of the stricture may be very short, panurethral strictures may also be seen. It has been shown that urethral stricture may be associated with resection duration, catheter type, catheterization duration, catheter diameter, pathology result, and urinary infection, either singly or as a combination of several of these.[8] However, no study comparing urethral length and stricture development could be found in the literature, so this research was

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planned based on the thought that urethral length may contribute to the development of stricture after surgical procedures.

In this study, patients who underwent bipolar TURP in our clinic as surgical treatment for BPH were evaluated. The patients were grouped according to the development or not of postoperative urethral stricture. These two groups were compared in respect of patient characteristics, total prostate specific antigen (tPSA), prostate volume, resection amount, resection amounts per minute, changes in hemoglobin values after the procedure, the pre-post procedure change in the amount of post-micturition residual urine (PMR), the pre-post procedure change in urine peak flow (Qmax), and urethral length.

2. Materials and methods

The study was a retrospective, that included patients who underwent bipolar TURP because of BPH unresponsive to medical treatment in the Urology Department of Baskent University between May 2019 and February 2020. All the patient information was obtained from the hospital records. The absence of previous urethral stricture in all patients was confirmed by cystoscopy before TURP. Each patient underwent urethra calibration with 30f bougie dilators during TURP. The patients with available data were separated into two groups as those who developed and did not develop urethral stricture. The diagnosis of urethral stricture was made during cystoscopy performed on those who had difficulty urinating after the TURP. A record was made for each patient of the patient characteristics, tPSA, operating time, prostate volume, resection amount, resection amounts per minute, changes in hemoglobin values after the procedure, the pre-post procedure change in the amount of PMR, the pre-post procedure change in Qmax, and urethral length. The first postoperative evaluations were made at 6 weeks postoperatively.

The surgical procedure was performed using an Olympus® bipolar resection device (Olympus Europa SE & Co., Hamburg, Germany). It was ensured that the temperature of the irrigation fluid used in the surgical procedure was equal to room temperature. Postoperatively, a 22F 3-way Rusch® Gold Foley catheter (Teleflex Medical, Republic of Ireland) was placed as standard. Urethral length was measured as shown in Figure 1, by placing the catheter and holding the penis stretched with the patient in the lithotomy position immediately before starting surgery, and this measurement was recorded [|CD| = |AB| - (|AC| + |BD|)].

2.1. Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 25.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables were stated as mean±standard deviation (SD) values depending on normality assumptions, and categorical variables as number (n) and percentage (%). Conformity of the variables to normal distribution was examined with the Shapiro-Wilk test. As the data were not normally distributed, differences between the groups were examined with the Mann Whitney U-test. Risk factors affecting the development of urethral stricture were evaluated with Stepwise Binary Logistic Regression analysis. Type I error probability was defined as 0.05 in all the analyses

3. Results

Evaluation was made of 127 patients, comprising 17 (13,4%) who developed urethral stricture and 110 (86,6%) who did not develop urethral stricture. The descriptive characteristics and postoperative values of the patients are shown in Table 1. With the exception of age, no significant difference was determined between the groups in respect of height, weight, body mass index, preoperative tPSA values, prostate volume, operating time, amount of tissue resected, resection rate, change in hemoglobin, and changes in PMR urine.

The mean follow-up period was 11.8±8.01 months. At the 6-week postoperative examination, the change in Qmax values was observed to be statistically significantly lower in the group that developed urethral stricture [respectively 15 (-1 - 29) ml/sec, 11 ml/sec (-5 - 19) ml/sec; p=0.027]. A difference of 1ml/sec in the Qmax change was seen to increase the risk of urethral stricture development 1.1-fold (96% confidence interval (CI): 1.017-1.200). Urethral length was determined to be median 23 cm (19 - 28.9 cm) in the group that developed stricture, and median 21.4 cm (16.7 - 27.3 cm) in the group that did not develop stricture, and the difference between the groups was statistically significant (p=0.002). An increase of 1cm in urethral length was determined to increase the risk of developing urethral stricture 1.44-fold (96% CI: 1.108-1.872).

Table 1

Comparison of patients with and without urethral stricture after TURP

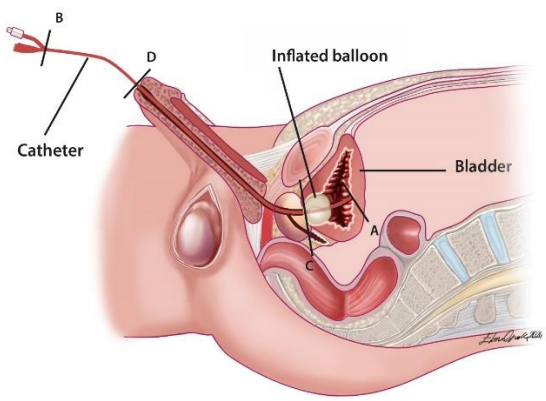
	Developing Urethra Stricture (n=17)	Not Developing Urethra Stricture (n=127)	p
Age	67 (54-75)	68 (52-93)	0,045*
Height (mt)	1.77 (1.65 - 1.92)	1.73 (1.55 - 1.86)	0.311
Weight (kg)	81 (66 - 123)	78 (50 - 120)	0.191
BMI (kg/m^2)	27.68 (21.68 - 37.87)	26.55 (19.53 - 41.52)	0.376
tPSA (ng/dl)	2.94 (0.5 - 13.71)	2.89 (0.45 - 176)	0.715
Duration of operation (min)	50 (30 - 155)	58.5 (20 - 178)	0.339
Prostat Volume (ml)	72 (23-140)	65 (24-180)	0,676
Tissue Amount (gr)	18.3 (4.3 - 60)	17.4 (3.2 - 118.7)	0.804
Resection Rate (gr/min)	0.28 (0.1 – 0.57)	0.27 (0.09 - 0.74)	0.463
Qmax change (ml/sn)	11 (-5 - 19)	15 (-1 - 29)	0.027*
Hemoglobin Change (gr/dL)	-0.6 (-3.4 – 0.4)	-1.1 (-6.6 – 2.1)	0.316
PMR change (ml)	-65 (-470 - 50)	-140 (-1485 - 25)	0.097
Urethra Length (cm)	23 (19 - 28.9)	21.4 (16.7 - 27.3)	0.002*

mt: meter, kg: kilogram, ng: nanogram, dl: deciliter, min: minute, ml: mililiter, gr: gram, sn: second, cm: centimeter
**p<0.05*

4. Discussion

Benign prostate hyperplasia (BPH), which is one of the most common causes of lower urinary tract symptoms (LUTS), is a frequently seen condition. TURP is the gold standard surgical treatment method for patients with LUTS unresponsive to medical treatment and for those with predominantly evacuation symptoms. In a 1962 study by Holtgreve et al. of a series of 2105 cases in the period when

Figure 1
Measurement of urethra length



TURP first came into use, it is striking that the mortality rate associated with TURP was reported to be 2.5%[9]. In subsequent years, this rate reduced dramatically, reaching 0.25% in recent series[9].

The main reason for this decrease is the developments in anaesthesia and surgical procedures.[10] Although TURP-related complications have gradually decreased, technical complications are still seen such as bleeding, capsule perforation, TUR syndrome, clot retention, urinary system infection, hydronephrosis, urosepsis, and incontinence. In addition to these complications, cardiac arrhythmia, myocardial infarctus, pulmonary embolism, pneumonia, chronic obstructive pulmonary disease, and postoperative deep vein thrombosis have been documented in 0.5%-11% of patients.[10]

To the best of our knowledge, there is no direct formula providing the actual urethral length in adults. However, Sreekanth et al. demonstrated a formula for urethral length according to age, height, and weight in children aged 1-15 years[11]. The urethral length was first measured with the help of a Foley catheter, then formulised according to height and weight. However, when compared according to the results of the current study, this formulation was not seen to provide an accurate result in adults. As seen in the current study, the real urethral length could be obtained with direct measurements using a urethral catheter.

Another important long-term complication of TURP is generally a difficulty in urinating because of urethral strictures or narrowness of the bladder neck. Urethral stricture is usually due to injury to the urethral mucosa and surrounding tissues. Urethral strictures can be classified as anterior and posterior, with anterior comprising 92.2%. Most occur in the bulbar urethra alone (46.9%), followed by in the penile urethra alone (30.5%), or bulbar and penile strictures (9.9%), and finally, pan-urethral strictures (4.9%).[12] In literature, the rate of urethral stricture has been reported to vary between 2.2% and 9.8%, and the rate of bladder neck stricture as 0.3%-9.2%.[13] In the current study, these rates were higher at 13.2%. Meatal strictures are generally due to incompatibility between the urethral meatus diameter and the device diameter, and bulbar strictures form because of monopolar current leakage as a result of insufficient isolation by lubrication gel. To prevent the development of urethral stricture, sufficient lubricant must be applied to the urethra and along the outer sheath of the resectoscope, and lubricant must be re-applied when the resection time is long.

Instead of the use of monopolar energy, bipolar energy is currently used. Tefekli et al. suggested that bipolar TURP caused a higher incidence of stricture than monopolar TURP[14]. Hueber et al. compared the results of 43 males at 6 months postoperatively and reported no significant difference between the two techniques.[15] In another study with a short follow-up period, Mamoulakis et al. reported that another intervention was necessary because of urethral stricture in 12 (9.9%) of the 121 patients in the monopolar TURP arm and in 20 (14.8%) of the 135 patients in the bipolar TURP arm (p=0.32).[16] In a review comparing bipolar and monopolar TURP results, Sinha et al. reported that from 9 studies that mentioned postoperative urethral stricture and bladder neck stricture, a significant increase in urethral stricture was only determined in the bipolar TURP group of a study by Stucki et al. (p=0.002).[17,18] Although the current does not pass through the urethra in bipolar TURP, there has been no significant decrease in the number of patients presenting with stricture. Urethral stricture can cause repeated urethral interventions or more costly urethroplasty operations for these patients. Therefore, it is recommended that a high current should be avoided during resection and urethra calibration with meatal or urethral dilatation should be performed before TURP.[19]

Despite standard surgical procedures performed with the same device and the same method, urethral strictures continue to be seen in patients. Tao et al. reported the development of urethral stricture in 29 (7.8%) of 373 patients.[20] A slow resection rate is seen as another risk factor as it is associated with poor surgical outcomes such as bleeding, prolonged operating time, more fluid leakage/absorption, and urethral mucosal damage, which are potential causes of urethral stricture[21]. However, in the current study, no significant difference was found between the two groups in respect of resection rates.

In the study by Tao et al., urethral length was not investigated as a cause. Although urethral mucosa rupture seems to be a plausible cause, it would not be wrong to think that urethral length could increase the probability of mucosal rupture. The presence of urethral mucosa rupture has been found to be an independent risk factor. When the integrity of the urethral mucosa is disrupted, it has been reported that there will be urine leakage below the epithelium, and consequently, there will be inflammation and scar formation.[20] However, there is also a study showing that the development of urethral stricture can be prevented with the suppression of inflammation with colchicine treatment.[22] In that study, the authors showed that stricture could be prevented by colchicine blocking the arachidonic acid lipoxygenase pathway, reducing inflammation and chemotaxia, preventing leukotriene formation and intervening in procollagen transcellular migration.

It has been reported that generally age is not a significant factor in urethral strictures developing after TURP.[23] In contrast, there is also a study reporting that patient age is a significant factor.[24] Balbay et al. determined the median age of patients to be 61.7 years (49-75 years) in those who developed urethral stricture after TURP, and 66.8 years (45-96 years) in those who did not develop stricture.[24] Similarly, our study concluded that age is an important factor for urethral stricture. The median age of the patients who developed stricture was determined to be younger, similar to the above-mentioned study.

To the best of our knowledge, there is no previous study in literature that has shown that urethral length contributes to urethral stricture developing after TURP. The relationship between an increase in urethral length and the development of urethral stricture can be considered a reason for the greater risk of urethral mucosal damage in patients with a long urethra. That the urethral length was greater in the group that developed stricture after surgery was an expected result in this study.

4.1. Limitation

The main limiting factor of this study seems to be that the surgical treatments were performed by different surgeons. In addition, there were very few subjects with urethral stricture. Therefore, there is a need for further studies with greater numbers of patients and a high level of evidence to confirm these findings.

5. Conclusion

The results of this study demonstrated that it would be beneficial to take more care in respect of the development of urethral stricture following TURP in cases where the resectoscope sheath is in contact with the urethral meatus, in other words in cases where urethral length is greater. To prevent the development of urethral stricture in these cases, attention must be paid to the frequent use of lubricating gel to the urethra, and urethra calibration before the procedure would also be useful in preventing stricture development.

Statement of ethics

The present study protocol was reviewed and approved by Baskent University Institutional Review Board and Ethics Committee (Project no: KA 19/93).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Eray Hasirci: Substantial contributions to the conception and design of the work; and the acquisition, analysis, and interpretation of data for the work. Drafting the work. Final approval of the version to be published. Responsibility for all aspects of ensuring questions regarding the accuracy of the work.

Enis Kervancioglu: Acquisition, reviewing the work critically for important intellectual content. Final approval of the version to be published. Responsibility for all aspects of ensuring questions regarding the accuracy of the work.

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Can Psoas muscle density predict the development of metastasis in non-metastatic adrenocortical carcinomas?

A CT-based AI-assisted automated segmentation analysis study

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Abstract

Aim: Our study aimed to investigate whether artificial intelligence-based body composition analysis can predict metastasis development during follow-up in patients with non-metastatic adrenocortical carcinoma (ACC) at the time of diagnosis.

Methods: Forty-five patients with non-metastatic ACC were included at the time of diagnosis. From the patients' non-contrast computed tomography (CT) scans, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), psoas area, psoas density, total muscle area, and total muscle density were automatically measured from sections taken at the level of the inferior endplate of the L3 vertebra. Patients were followed for developing liver, lung, and lymph node metastases. The relationship between body composition and liver and lymph node metastasis development was investigated. Propensity score matching (PSM) was performed for patients with metastases.

Results: Forty-five patients, 27 of whom were female, with non-metastatic ACC at the time of diagnosis, were included in the study. The mean age of the patients was 53±17.4 years. Significant differences were found between the groups that developed liver metastases and those that did not, and between the groups that developed lymph node metastases and those that did not, in terms of correct Psoas HU, left Psoas HU, PMD, Wall Muscle HU, and age ($p<0.05$). After applying PSM based on age, sex, and T stage, the odds ratio for psoas muscle density in predicting liver metastasis was found to be 0.898, 95% CI(0.828-0.973) in the logistic regression analysis.

Conclusions: Psoas muscle density may be a potential biomarker for predicting metastasis development in patients with non-metastatic ACC.

Keywords: *Adrenocortical carcinoma, sarcopenia, metastasis, psoas muscle density, adipose tissue*

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and lethal malignancy. The incidence of ACC is reported as 1-2 per million population/year.[1,2] Complete surgical resection is the only potentially curative option for localized disease and reported 5-year survival rates following curative resection range from approximately 15-44%.[3] Despite the generally unfavorable prognosis of ACC, there is significant individual variability in disease progression, recurrence, and overall survival. Even in patients with stage 4 disease, survival ranges from a few months to several years. Exceptional cases of long-term survival with ACC diagnosis have been reported.[4] Despite these variations in survival, prognostic factors have not been definitively established. While patient age at diagnosis, tumor surgical resection, tumor growth rate, mitotic index, and high tumor index have been identified as risk factors for poor survival, a well-established system is not yet available.[5, 6]

Although ACC treatment has been advanced over the past years, options for advanced ACC still need to be improved.[7] Chemotherapy with the FIRM-ACT protocol is the current standard treatment.[8] While tyrosine kinase inhibitors and other targeted therapies have shown potential efficacy, novel therapeutic approaches are needed.[7] A better understanding of the molecular profile of ACC has pointed to a limited number of druggable molecular targets. Immunotherapy results are still unclear, as the tumor microenvironment and potential endocrine activity are complex.[3,8] Due to its relative rarity and heterogeneity, personalized treatment is becoming increasingly important.

Sarcopenia, defined as the progressive and generalized loss of muscle mass and function, is typically associated with aging, but ca-

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chexia in malignancy can also contribute to its development[9]. Furthermore, sarcopenia can be viewed as a surrogate for a patient's overall frailty, defined as a syndrome of physiological reserve loss, impaired homeostatic mechanisms, and vulnerability to adverse outcomes.[10] Studies have shown its utility as a tool to determine overall survival and prognosis in many malignancies. However, the number of studies investigating the relationship between sarcopenia and ACC is quite limited compared to other malignancies.[11,12]

In our study, considering the presence of tumor cachexia that can be observed in metastatic patients, we aimed to investigate the relationship between artificial intelligence-based body composition analysis and the development of metastases in non-metastatic ACC patients.

2. Materials and methods

2.1. Patient Selection

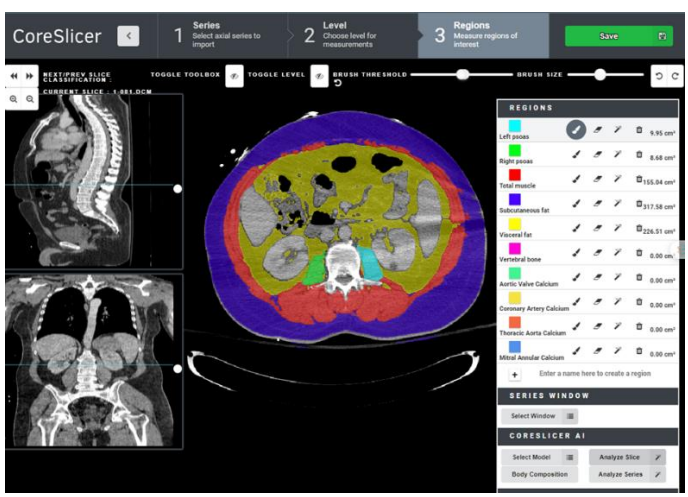
ACC patients from the Adrenal-ACC-Ki67-Seg dataset were included in the study (https://www.cancerimagingarchive.net). Patients with metastatic disease at the time of diagnosis were excluded. All 45 patients were included in the study. Patients in the dataset were followed between 2006 and 2018. The development of liver, lung, and lymph node metastases during follow-up was investigated. Local ethics committee approval was obtained (67-2024).

2.2. Body Composition Analysis

Contrast-enhanced CT images of the patients were uploaded to the open-source, web-based "CoreSlicer" tool [13]. Measurements were performed at the level of the L3 vertebra inferior endplate. Visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), psoas area, psoas density, total muscle area, and total muscle density were automatically measured. The measurements were performed by a radiologist with 10 years of experience. You can view the system interface in Figure 1.

Table 1

CoreSLicer user interface



2.3. Statistical Analysis

Continuous variables were reported as means (± standard deviation) and categorical variables as numbers (proportion). Normality tests were performed for continuous variables Kolmogorov-Smirnov and Shapiro-Wilk test. Comparisons between groups were performed using the following statistical tests: chi-square test for categorical variables, Student's t test for normal-distributed continuous variables, Mann-Whitney U test for non-normal-distributed continuous variables.

To minimize selection bias and adjust for imbalances between groups, we used 1:1 propensity score matching (PSM). The SPSS R plugin (SPSS R Essentials) was implemented for matching[14]. We used the SPSS 'PS Matching' feature to perform the propensity score-matched analysis. Matching factors included age, sex, and T stage. Patients who developed liver and lymph node metastases during follow-up and those who did not were 1:1 matched in a multivariate logistic analysis using stepwise regression based on a greedy matching algorithm with a caliper of 0.05 times the logit's standard deviation (SD).

Using logistic regression after PSM, the association between the development of metastases during follow-up and body composition parameters was investigated.

Table 1

Results of body composition analysis in patient groups with and without liver metastasis development during follow-up.

	Group	Mean± Sd	P value
Left psoas area (cm^2)	No (n:32)	9.71 ±2,99	0.148
	Yes (n:13)	8.28 ± 2,81	
Left psoas density (HU)	No (n:32)	46.11±10.40	**0.006**
	Yes (n:13)	36.66 ±8.71	
Right psoas area (cm^2)	No (n:32)	9.58±2.97	0.127
	Yes (n:13)	8.06±2.97	
Right psoas density (HU)	No (n:32)	46.12±9.395	**0.004**
	Yes (n:13)	36.70±9.01	
Abdominal wall muscle area (cm^2)	No (n:32)	123.06±24.91	0.939
	Yes (n:13)	122.32±37.99	
Abdominal wall muscle density (HU)	No (n:32)	32.84±12.57	**0.014**
	Yes (n:13)	22.37±12.24	
Subcutaneous adipose tissue area (cm^2)	No (n:32)	264.48±161.460	0.882
	Yes (n:13)	271.67±95.42	
Subcutaneous adipose tissue density (HU)	No (n:32)	-98.29±12.73	0.509
	Yes (n:13)	-100.82±7.70	
Visseral adipose tissue area (cm^2)	No (n:32)	174.15±114.11	0.119
	Yes (n:13)	234.18±116.40	
Visseral adipose tissue density(HU)	No (n:32)	-83.49±23.90	0.336
	Yes (n:13)	-90.19±9.94	
Psoas muscle density (HU)	No (n:32)	45.93±9.62	**0.005**
	Yes (n:13)	36.79±8.54	
Age	No (n:32)	50.47±13.32	**0.041**
	Yes (n:13)	59.46±12.05	

3. Results

This study included 45 patients, 27 female and 18 male, with non-metastatic disease at the time of diagnosis. The mean age of the patients was 53 ± 17.4 years. At the time of diagnosis, 4 patients were stage T1, 19 were stage T2, and 22 were stage T3. During follow-up, 13 patients developed liver metastases, 6 developed lymph node metastases, 15 developed lung metastases, and 4 developed bone metastases.

No association was found between body composition parameters and the development of lung and bone metastases during follow-up. Significant differences were found between the group that developed liver metastases during follow-up and the group that did not in terms of Right Psoas HU, Left Psoas HU, PMD, Wall Muscle HU, and age (p: 0.004, p: 0.006, p: 0.005, p: 0.041, respectively). Significant differences were found between the group that developed lymph node metastases during follow-up and the group that did not in terms of Right Psoas HU, Left Psoas HU, and PMD (p: 0.037, p: 0.019, p: 0.024, respectively). Please see Tables 1 and 2 for detailed information.

To determine the net effect of psoas muscle density, a logistic regression analysis was performed on 13 patients with liver metastases and 13 without after matching for age, sex, and T stage. The odds ratio was 0.898, 95% CI (0.828-0.973). A similar logistic regression analysis was performed on 6 patients with lymph node metastases and 6 without, resulting in an odds ratio of 0.892, 95% CI (0.803-0.991). Please see Table 3 for details.

Table 2

Results of body composition analysis in patient groups with and without lymph node metastasis development during follow-up

	Group	Mean± Sd	P
Lef psoas area (cm^2)	No (n:39)	9.44±3.12	0.419
	Yes (n:6)	8.37±1.82	
Left psoas density Hu	No (n:39)	44.68±10.48	**0.037**
	Yes (n:6)	34.93±9.16	
Right psoas area (cm^2)	No (n:39)	9.23±2.30	0.618
	Yes (n:6)	8.56±3.38	
Right psoas density (HU)	No (n:39)	44.77±9.52	**0.019**
	Yes (n:6)	34.47±10.35	
Abdominal wall muscle area(cm^2)	No (n:39)	122.89±27.80	0.979
	Yes (n:6)	122.56±37.93	
Abdominal wall muscle density (HU)	No (n39)	30.95±13.15	0.146
	Yes (n:6)	22.46±12.37	
Subcutaneous adipose tissue area (cm^2)	No (n:39)	272.06±151.40	0.521
	Yes (n:6)	230.79±87.13	
Subcutaneous adipose tissue density (HU)	No (n:39)	-98.40±12.084	0.360
	Yes (n:6)	-103.06 ±5.09	
Visseral adipose tissue area (cm^2)	No (n:39)	185.96±117.99	0.424
	Yes (n:6)	227.45±110.94	
Visseral adipose tissue density (HU)	No (n:39)	-83.92±22.03	0.222
	Yes (n:6)	-95.24±6.45	
Psoas muscle density (HU)	No (n:39)	44.61±9.67	**0.024**
	Yes (n:6)	34.69±9.51	
Age	No (n:39)	50.47±3.12	0.358
	Yes (n:6)	59.46±1.82	

Table 3

Logistic regression analysis with matched patients after Propensity-Score Matching

	Odds Ratio (95% CI)	p
Follow up- Liver Metastasis	0.898 %95CI (0.828- 0.973)	0.009
Follow up- Lymph node metastasis	0.892 %95CI (0.803- 0.991)	0.034

4. Discussion

This study investigated the potential utility of artificial intelligence-assisted automated segmentation and body composition analysis in predicting metastatic progression in patients with non-metastatic adrenocortical carcinoma (ACC). Our findings revealed a significant association between psoas muscle density and liver and lymph node metastasis development. These results suggest that psoas muscle density may be a viable biomarker for predicting prognosis in ACC.

Significant differences were observed in factors such as psoas muscle density and age between patients who developed liver and lymph node metastases during follow-up. This observation suggests that muscle density may be sensitive to specific metastatic patterns. Patients who developed liver metastases exhibited significant reductions in right and left psoas HU values (p:0.004 and p:0.006, respectively). Similarly, lower psoas muscle density was observed in patients who developed lymph node metastases (p:0.037 and p:0.019, respectively).

Logistic regression analyses conducted on patients matched for factors such as age, sex, and T stage revealed that psoas muscle density holds potential as a predictor for the development of liver and lymph node metastases. Specifically, the odds ratio for liver metastasis was found to be 0.898 (95% CI: 0.828-0.973), and for lymph node metastasis, it was 0.892 (95% CI: 0.803-0.991). These results suggest that low muscle density is associated with an increased risk of metastasis.

Adrenocortical carcinoma (ACC) is a rare malignancy often associated with a poor prognosis. Treatment options are limited, and significant individual variability is observed in disease progression and survival. Therefore, the identification of novel biomarkers capable of better predicting disease prognosis is of paramount importance. Sarcopenia has been recognized as a significant factor in determining overall survival and prognosis in various malignancies.[15] However, studies investigating the relationship between ACC and sarcopenia are limited.[12] Sarcopenia is a significant factor that can arise in association with malignancies and is known to impact overall survival and prognosis in various cancer types. While often characterized as an age-related condition, sarcopenia is also associated with malignancy-associated cachexia. Loss of muscle mass and function can negatively affect patients' physiological reserves and overall health status, which is linked to poor prognosis in malignancies[15]. In ACC patients, as in other similar malignancies, cancer cachexia typically manifests in the advanced stages of the disease. Cachexia is characterized by progressive loss of body weight, including skeletal muscle mass or sarcopenia, due to systemic inflammation and cannot be fully reversed by conventional nutritional support.[16] The development of sarcopenia in ACC patients, in addition to causing a decrease in muscle mass, also leads to a reduction in muscle density. This decrease in muscle density suggests its potential as a prognos-

tic factor in predicting metastasis development.[17]

A previous study by Miller et al. [11] reported that central sarcopenia was associated with poor survival and that increased intra-abdominal fat reduced survival in ACC patients. This study suggests that psoas muscle density is an essential factor to consider in the prognosis of ACC. De Jong et al.[12] reported that sarcopenia reduced survival after ACC surgery. These findings suggest that muscle density may be associated with the development of metastases. Low psoas muscle density can be associated with decreased physiological reserves and increased patient frailty. This can be considered an adverse prognostic factor for metastasis development and disease progression. Furthermore, the measurement of psoas muscle density is non-invasive and easily applicable, making its integration into clinical practice feasible.

4.1. Limitation

The major limitation of this study is the small sample size. Limited to only 45 patients, this study must be validated in more extensive and diverse populations. Furthermore, due to its retrospective nature, it requires support from prospective studies. Future research should investigate how AI-assisted segmentation methods can be integrated into ACC management in conjunction with other prognostic factors. Fassnacht et al.[8] have highlighted the need for new therapeutic approaches in treating ACC and explored the potential of immunotherapy. Using psoas muscle density as a prognostic biomarker could be crucial for personalizing treatment strategies.

5. Conclusion

In conclusion, psoas muscle density may serve as a biomarker for predicting the development of metastases during follow-up in patients with non-metastatic ACC. This finding could be a significant step towards improving ACC's prognosis and offering patients more personalized treatment approaches. However, validation with more extensive and prospective studies is warranted.

Statement of ethics

The present study protocol was reviewed and approved by Adana City Hospital Ethics Committee ((67-2024)).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Emin DEMIREL: Conceptualization, Methodology, Software, Data curation, Writing - original draft. Okan DILEK: Formal analysis, Conceptualization, Writing, Supervision,

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Enhancing Hematopoietic Stem Cell Transplantation Success: The Crucial Role of Architectural Design in Transplant Units and Hematology Departments

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Abstract

Aim: This paper aims to explore the critical role of architectural design in Hematopoietic Stem Cell Transplantation (HSCT) procedures, focusing on how various aspects of design influence patient outcomes, staff efficiency, infection control, and overall safety. The study seeks to understand how the physical environment impacts both the immediate and long-term recovery of patients undergoing HSCT and to advocate for design principles that enhance patient and caregiver experiences.

Discussion: Hematopoietic Stem Cell Transplantation (HSCT) has emerged as a vital therapeutic modality for a diverse spectrum of hematological disorders and malignancies. As medical and technological advancements continue to evolve, the significance of the physical environment in which HSCT procedures are conducted becomes increasingly evident. This paper delves into how architectural design affects patient well-being, staff efficiency, and infection control, emphasizing the importance of creating environments that support psychological well-being. It examines the impact of design on infection prevention, safety during emergencies, and the overall efficiency of healthcare delivery. The discussion also highlights the role of sustainability and green design principles in minimizing the environmental footprint while promoting patient recovery.

Conclusions: The paper concludes that architectural design plays a transformative role in enhancing patient experiences and healthcare outcomes in HSCT settings. It underscores the need for a patient-centric approach to design that integrates wellness-focused elements and advanced technology. The study advocates for a collaborative effort among healthcare institutions, architects, designers, and policymakers to create supportive, efficient, and sustainable healthcare environments. By prioritizing these design considerations, healthcare environments can significantly improve the HSCT journey and contribute to the broader realm of healthcare excellence.

Keywords: *Hematopoietic Stem Cell Transplantation, Architectural Design, Healthcare Environment, Patient-Centered Care, Sustainability in Healthcare*

1. Introduction

Hematopoietic stem cell transplantation (HSCT) has emerged as a pivotal therapeutic intervention in the management of various hematological disorders and malignancies. Over the past few decades, significant strides in medical science and technology have elevated the success rates of HSCT, transforming it into a life-saving procedure for countless patients.[1,2] While medical advancements continue to be at the forefront of improving patient outcomes, this manuscript aims to shed light on a rather underexplored dimension of HSCT - the architectural design of the facilities where these crucial procedures take place.[3]

In the realm of healthcare, architectural design has traditionally played a subsidiary role, often overshadowed by the prominence of clinical expertise and technological innovation.[4] However, as the landscape of modern medicine evolves, so does our understanding of the multifaceted factors that influence patient care. One such factor, which has gained recognition in recent years, is the physical environment in which healthcare interventions occur. In the context of HSCT, the architectural design of transplant units and hematology departments emerges as a critical determinant of treatment success and overall healthcare quality.[5,6]

Historically, healthcare architecture has primarily focused on functional aspects, such as efficient space utilization and adherence

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to regulatory standards. While these considerations are undeniably important, they only scratch the surface of what a well-thought-out architectural design can offer.[7-9] This review ventures into the intricate interplay between architectural design and the intricate dynamics of HSCT, illustrating how it extends beyond mere aesthetics and convenience to significantly impact patient outcomes, staff efficiency, infection control, and, ultimately, the overall quality of healthcare delivery.

The overarching objective of this exploration is to underscore the pivotal role that architectural design plays within the realm of HSCT. It is a call to recognize the intricate synergy between medical science and the physical spaces where it is practiced. By delving into the nuances of design, this manuscript seeks to provide invaluable insights into creating environments that are not merely functional but supportive of the holistic well-being of patients and healthcare professionals alike. Ultimately, our aim is to contribute to the collective endeavor of refining transplantation outcomes and elevating the standard of care provided in the challenging field of hematopoietic cell transplantation.

2. Patient-Centered Design

In the domain of healthcare, the concept of patient-centered care has become a guiding principle, emphasizing the importance of tailoring medical services to meet individual patient needs.[10] In this context, architectural design takes on a pivotal role in facilitating patient-centered care within HSCT units and hematology departments.[11,12] This section delves into the intricate facets of patient-centered design, highlighting its profound impact on patient well-being and, consequently, treatment outcomes.

2.1. Designing Patient Rooms for Comfort and Psychological Well-being

The patient room is the primary focus of the patient's experience within a healthcare facility.[13] As such, its design should prioritize patient comfort and psychological well-being. Considerations extend beyond mere functionality; they encompass creating an environment that fosters a sense of security, reduces anxiety, and promotes optimism during the often-arduous journey of HSCT.[14-17]

Patient rooms should be spacious, allowing for ease of movement for both patients and healthcare providers. Adequate space also accommodates the presence of family members, a crucial source of emotional support during the transplantation process. Moreover, ergonomic furniture and furnishings that prioritize patient comfort are essential. These elements contribute not only to physical comfort but also to a sense of normalcy in an otherwise clinical setting.[18]

The design should also embrace elements that evoke a sense of normalcy and homeliness. Personalization options, such as space for personal belongings and artwork, can significantly enhance the patient's sense of control and identity within the sterile hospital environment.[19] Additionally, the arrangement of furniture and the inclusion of spaces for relaxation contribute to an environment conducive to emotional healing and recovery.[20,21]

2.2. The Importance of Natural Light, Views, and Privacy

Natural light has been shown to have a profound impact on patient outcomes. It can positively influence mood, circadian rhythms, and overall well-being. Hence, patient rooms should be designed to maximize access to natural light. Large windows, strategically placed to provide both privacy and views of nature, can significantly enhance the patient's experience. Ensuring that patients have the option to control the amount of light in their rooms through window treatments adds an extra layer of patient-centeredness. Privacy, another critical consideration, must be carefully balanced with the desire for natural light and views. Ensuring that patients have a private space where they can receive visitors and engage in confidential discussions with healthcare providers is essential. Thus, thoughtful design should provide for both privacy and connection to the outside world.[22-24]

2.3. Ergonomic Considerations for Patient Mobility and Rehabilitation Spaces

The architectural design of HSCT units and hematology departments should extend its patient-centered focus to include ergonomic considerations. Patients undergoing HSCT often face physical challenges, including fatigue and reduced mobility. In response, the layout of patient rooms and common areas should prioritize accessibility, with attention to features such as grab bars, non-slip flooring, and easily accessible amenities. Rehabilitation spaces, both within patient rooms and communal areas, are vital for supporting patients' physical recovery. These spaces should be equipped with appropriate exercise equipment and aids, facilitating the rehabilitation process. Additionally, their design should promote safety and ease of use, ensuring that patients can engage in exercises independently or with the guidance of healthcare professionals.[25,26]

It should be taken into account that patient-centered design within HSCT units and hematology departments extends beyond aesthetics; it is a fundamental component of patient care. Prioritizing patient comfort, psychological well-being, access to natural light, privacy, and ergonomic considerations not only enhances the patient experience but also contributes to better treatment outcomes. Section 2 highlights the crucial role of architectural design in creating environments that foster patient-centered care in the context of hematopoietic cell transplantation.

3. Infection Control and Cleanliness

In the realm of healthcare, where patient well-being and recovery hinge on the management of complex diseases, the role of architectural design extends beyond aesthetics and comfort. Section 3 delves into the critical domain of infection control and cleanliness within HSCT units and hematology departments. These settings demand rigorous measures to mitigate the risk of infection, and the architectural design plays a pivotal role in achieving this objective.

3.1. The Impact of Air Quality and Ventilation Systems

Effective infection control begins with the management of air quality within healthcare facilities.[27] In HSCT units and hematology departments, the immunocompromised status of many patients heightens their vulnerability to airborne pathogens. Consequently, meticulous attention to air quality and ventilation systems is paramount. Architectural design should prioritize the installation of high-efficiency particulate air (HEPA) filtration systems.[28] These systems effectively remove airborne particles, including microorganisms, thus reducing the risk of cross-contamination. The strategic placement of air supply and exhaust vents, along with proper airflow direction, can further optimize air quality within patient rooms and common areas.[29-31]

3.2. Materials and Surfaces that Facilitate Effective Sanitation

Infection control extends beyond the air to encompass surfaces and materials within healthcare environments. The choice of materials should prioritize those that are easy to clean and resistant to harboring pathogens. Non-porous surfaces, such as stainless steel and laminates, are preferred for countertops and furniture, as they can be readily disinfected. Additionally, the design should minimize the presence of crevices, seams, and other areas where microbes can accumulate and proliferate. Seamless surfaces and well-sealed joints not only enhance sanitation efforts but also simplify maintenance procedures, ultimately contributing to a safer and cleaner environment.[32-34]

3.3. Spatial Planning to Reduce the Risk of Cross-Contamination

Spatial planning within HSCT units and hematology departments plays a pivotal role in infection control. The layout of patient rooms, common areas, and workflow pathways should be meticulously designed to minimize the risk of cross-contamination. This includes the strategic separation of potentially infectious zones from clean areas. The architectural design should incorporate principles of zoning, with clear demarcations between high-risk and low-risk areas.[35] Moreover, the placement of hand hygiene stations and personal protective equipment (PPE) dispensers should be well-distributed, ensuring ready access for both patients and healthcare providers.[36] Such considerations foster adherence to infection control protocols, reducing the likelihood of transmission.

In conclusion, the indispensable role of architectural design in infection control and cleanliness within HSCT units and hematology departments. The meticulous design of air quality systems, the selection of appropriate materials, and spatial planning that mitigates the risk of cross-contamination are fundamental elements in safeguarding the health and well-being of both patients and healthcare providers.[37,38] By prioritizing these aspects, healthcare facilities can create environments that are conducive to the delivery of safe and effective care, particularly for patients undergoing hematopoietic cell transplantation.

4. Workflow Efficiency

Efficiency in healthcare delivery is a cardinal principle that resonates throughout the medical field. Within the context of HSCT units and hematology, radiology, interventional radiology departments, laboratory for blood tests and microbiology, blood bank and intensive care unit[39], this principle takes on heightened significance, given the complexity of care required and the imperative for timely interventions. Section 4 examines the pivotal role of architectural design in enhancing workflow efficiency, thereby optimizing patient care and improving overall healthcare quality.

4.1. Streamlining the Patient Journey Within the Department

Patient care within HSCT units and hematology and the other departments involves a coordinated and multifaceted journey that spans diagnostics, treatment, monitoring, and recovery.[40] The architectural design of these departments should prioritize the streamlining of this patient journey. This entails careful attention to the layout of spaces and their interconnections. Efficient spatial planning should minimize patient travel distances, reducing the potential for delays in care. Furthermore, the design should facilitate the logical progression of steps in the patient's journey, ensuring that patients move seamlessly from one phase of care to another. This not only enhances patient experience but also contributes to more timely interventions and better clinical outcomes.

4.2. Ensuring Easy Access to Critical Equipment and Supplies

Accessibility to critical equipment and supplies is foundational to efficient healthcare delivery. Within HSCT units and hematology departments, where precise and often rapid interventions are required, the architectural design should ensure easy access to these essentials. Strategically positioned supply storage areas and equipment hubs can expedite care delivery. Furthermore, the design should consider the proximity of patient rooms to supply and equipment storage, minimizing the time spent retrieving necessary items. This not only optimizes workflow but also enhances staff productivity, allowing healthcare providers to allocate more time to direct patient care.[41-43]

4.3. Staff Workstations and Their Influence on Communication and Collaboration

The architectural design should also prioritize staff workstations as hubs of communication and collaboration. Effective teamwork among healthcare providers is vital for delivering high-quality care within HSCT units and hematology departments. Workstations should be strategically positioned to foster communication and information sharing.[44,45] Considerations should include ergonomic workstation design, enabling staff to access patient information, communicate with colleagues, and coordinate care efficiently. Additionally, technology integration, such as electronic health record systems, should be seamlessly incorporated into the design to enhance data accessibility and facilitate real-time decision-making.[46]

In summary, the paramount importance of workflow efficiency within HSCT units and hematology and the other departments elucidates the role of architectural design in achieving this goal. Streamlining the patient journey, ensuring easy access to essential resources, and fostering effective communication and collaboration are pivotal aspects of architectural design that contribute not only to the optimization of care delivery but also to the enhancement of patient outcomes45. By embracing these principles, healthcare facilities can create environments that support the seamless provision of care for patients undergoing hematopoietic cell transplantation.

5. Safety and Emergency Preparedness

The safety of patients and healthcare providers is a paramount concern within HSCT units and hematology departments. These settings often deal with vulnerable patient populations, making preparedness for emergencies a critical imperative.[47-49] Section 5 delves into the role of architectural design in enhancing safety and emergency preparedness, highlighting design features and considerations that contribute to a secure healthcare environment.

Patient and staff safety is the foundation upon which quality healthcare is built. Architectural design plays a pivotal role in incorporating features that enhance safety within HSCT units and hematology departments. One essential aspect is the minimization of physical hazards. Flooring materials should be slip-resistant to prevent falls, and corridors should be designed to accommodate the safe passage of beds and equipment. Furthermore, the design should minimize sharp edges and protrusions that could pose risks to patients and staff.[50] This focus on safety extends to fixtures and furnishings within patient rooms, where the selection of appropriate materials can reduce the risk of injuries.

In the event of an emergency, rapid and safe evacuation is paramount. Architectural design should incorporate clear and well-marked evacuation routes, ensuring that patients and staff can exit the premises swiftly and safely. This includes the provision of accessible ramps and elevators for patients with mobility challenges. Additionally, the design should consider the location of emergency exits in relation to patient rooms and common areas. These exits should be strategically placed to minimize travel distances in the event of an evacuation, thus optimizing safety during high-stress situations.

The integration of technology is indispensable in modern healthcare settings, particularly in enhancing safety and emergency response. Architectural design should encompass the installation of advanced technology systems that support rapid response and crisis management. These systems may include fire alarms, smoke detectors, and automated notification systems that alert staff in case of emergencies. Video surveillance and access control systems can further enhance security within the facility. The seamless integration of these technologies into the architectural design ensures that safety measures are not only effective but also unobtrusive, preserving the healing environment.

It can be said that the pivotal role of architectural design in ensuring safety and emergency preparedness within HSCT units and he-

matology departments. Design features that enhance patient and staff safety, well-planned evacuation routes, and the integration of advanced technology collectively contribute to a healthcare environment that is resilient in the face of unexpected challenges. By prioritizing these aspects, healthcare facilities can uphold their commitment to safeguarding the well-being of all individuals within their care, even in the most demanding of circumstances.

6. Psychological Support and Well-Being

In the complex and often emotionally challenging world of HSCT units and hematology departments, the importance of psychological support and well-being cannot be overstated. Section 6 explores the role of architectural design in fostering psychological support and well-being for patients and their caregivers. This section delves into the profound impact of design on reducing stress, promoting healing, and enhancing the overall quality of care. The experience of undergoing HSCT is fraught with physical and emotional challenges, not only for patients but also for their caregivers.[51-54] Architectural design can significantly contribute to stress reduction by creating environments that exude tranquility and comfort. Patient rooms should be designed with an understanding of the emotional needs of patients and their families. Thoughtful incorporation of soothing colors, artwork, and nature elements can create a calming ambiance. Acoustic considerations, such as soundproofing and noise reduction, further promote a peaceful environment. Waiting areas and communal spaces should also be designed with stress reduction in mind. Comfortable seating, access to natural light, and aesthetically pleasing surroundings can alleviate anxiety and foster a sense of well-being for both patients and caregivers.

Psychological well-being thrives in environments that offer spaces for relaxation, meditation, and emotional support.[55] Architectural design should allocate areas within HSCT units and hematology departments for these purposes. Quiet rooms or meditation spaces can provide patients and caregivers with a refuge for solitude and reflection. Such spaces should be designed with tranquility in mind, incorporating elements like soft lighting[56,57], comfortable seating, and minimal distractions. In addition to individual spaces, support groups, and therapeutic interventions are essential. These spaces should be flexible in design, accommodating various activities while maintaining a sense of warmth and comfort.

The integration of art and nature elements into architectural design can be a powerful tool for enhancing psychological well-being. Artwork, whether in the form of paintings, sculptures, or installations, can serve as a source of inspiration and distraction during challenging times. Nature elements, such as indoor gardens or views of green spaces, bring the healing power of the outdoors into the healthcare environment.[58] Biophilic design principles, which connect people with nature through design, can have a profound impact on reducing stress and promoting emotional well-being. In conclusion, the crucial role of architectural design in providing psychological support and well-being within HSCT units and hematology departments. By creating environments that reduce stress, offer spaces for relaxation and emotional support, and incorporate art and nature elements, healthcare facilities can significantly enhance the overall experience of patients and caregivers.[59,60] These design considerations not only contribute to improved mental health but also complement the clinical care provided, ultimately fostering a holistic approach to patient well-being in the context of hematopoietic cell transplantation.

7. Sustainability and Green Design

In today's healthcare landscape, the integration of sustainable and green design principles is no longer a mere trend but a pressing necessity. Section 7 delves into the significance of sustainability within HSCT units and hematology departments, elucidating the profound implications of architectural design on environmental responsibility and patient well-being. The healthcare sector, including HSCT units and hematology departments, is a significant contributor to environmental impacts, such as energy consumption, waste generation, and resource depletion. Recognizing this, healthcare facilities are increasingly embracing sustainable practices to mitigate their environmental footprint. Architectural design is a pivotal aspect of this endeavor. Sustainable healthcare design not only reduces negative environmental effects but also aligns with the ethical and social responsibilities of healthcare organizations.[61-64] By reducing energy consumption, conserving resources, and minimizing waste generation, green design promotes environmental stewardship while also contributing to cost savings.

The choice of building materials and energy systems holds immense potential for sustainability within healthcare facilities. Architectural design should prioritize the use of sustainable building materials, such as recycled or renewable materials, low-emission finishes, and products with minimal environmental impact. Energy efficiency is another cornerstone of green design. The design should incorporate energy-efficient lighting, heating, ventilation, and air conditioning (HVAC) systems, which not only reduce operational costs but also lower greenhouse gas emissions. Passive design strategies, such as maximizing natural daylight and optimizing thermal performance, can further enhance energy efficiency. Beyond its environmental benefits, green design has the potential to positively influence patient recovery and well-being. Numerous studies have shown that access to natural light, views of greenery, and a connection to nature can accelerate healing, reduce stress, and improve patient satisfaction.[65-68] Architectural design should capitalize on these findings by incorporating biophilic design principles. These principles aim to reconnect patients and healthcare providers with nature through design elements like indoor gardens, green walls, and nature-inspired artwork. In addition to enhancing patient recovery, biophilic design can also contribute to the psychological well-being of staff and visitors.

There is an understanding that the critical role of sustainability and green design within HSCT units and hematology departments. By prioritizing sustainable building materials, energy-efficient systems, and biophilic design principles, healthcare facilities can not only reduce their environmental impact but also enhance patient recovery and well-being. The integration of sustainability into architectural design aligns with the evolving expectations of healthcare organizations and underscores the holistic approach required for excellence in hematopoietic cell transplantation care.

8. Future Directions

The landscape of healthcare is in a perpetual state of evolution, driven by scientific advancements, technological innovation, and changing patient needs. Section 9 delves into the future directions of architectural design within HSCT units and hematology departments. This section explores emerging trends, the integration of technology and artificial intelligence, and the evolving role of telemedicine in design considerations. The field of healthcare architecture is witnessing a paradigm shift in response to the evolving healthcare landscape. Emerging trends indicate a shift toward patient-centric design, where architectural solutions are tailored to in-

dividual patient needs. This includes the personalization of patient rooms and the incorporation of flexible spaces that can adapt to changing treatment modalities. Additionally, the concept of wellness-focused design is gaining prominence. Healthcare facilities are exploring ways to create environments that promote overall well-being, extending beyond the treatment of illness.[69-71] Elements like access to outdoor spaces, natural light, and spaces for physical activity are becoming integral to architectural design.

The rapid advancement of technology and artificial intelligence (AI) is poised to revolutionize healthcare architectural design. Smart buildings equipped with IoT (Internet of Things) sensors can monitor patient vital signs.[72,73], adjust environmental conditions, and streamline facility management. AI algorithms can analyze data from these sensors to predict and prevent equipment failures and optimize resource utilization. Furthermore, telehealth and telemedicine are becoming integral components of healthcare design. Architectural considerations now extend to creating spaces that facilitate remote consultations and virtual healthcare delivery. This includes the integration of telemedicine equipment and the design of private, secure spaces for virtual patient-provider interactions. Telemedicine has proven its value, especially during the global pandemic, and is expected to play an increasingly prominent role in healthcare delivery.[74,75] Architectural design must adapt to accommodate this shift. Spaces within HSCT units and hematology departments should be designed to support telehealth consultations, ensuring that patients have access to these services while maintaining privacy and confidentiality. Furthermore, telemedicine design considerations extend beyond patient spaces. Staff workstations and meeting rooms should be equipped with the necessary technology and infrastructure to facilitate remote consultations and collaborations with colleagues and specialists.

To end with, the future directions of architectural design within HSCT units and hematology departments. Emerging trends, the integration of technology and AI, and the expanding role of telemedicine underscore the need for flexibility and adaptability in healthcare architectural design. By embracing these evolving trends, healthcare facilities can continue to provide high-quality care while staying at the forefront of innovation in the field of hematopoietic cell transplantation.

9. Conclusion

In the ever-evolving landscape of healthcare, the architectural design of HSCT units and hematology departments has emerged as a dynamic and indispensable factor influencing patient outcomes, healthcare quality, and environmental responsibility. This manuscript has journeyed through the multifaceted aspects of architectural design within these critical healthcare settings, underscoring its pivotal role in shaping the future of HSCT care and beyond. Throughout this exploration, it becomes abundantly clear that architectural design transcends its conventional role as a functional necessity. Instead, it emerges as an agent of profound transformation, capable of elevating the standards of care and the experiences of patients, caregivers, and healthcare providers alike. Architectural design contributes to patient-centered care by creating environments that prioritize comfort, natural light, and privacy. It empowers infection control and cleanliness through meticulous planning and the integration of advanced ventilation systems. Workflow efficiency is optimized by thoughtfully designed spaces that facilitate the delivery of timely care. Safety and emergency preparedness are bolstered by design features that prioritize the well-being of all occupants.

Furthermore, architectural design becomes a catalyst for psychological support and well-being. By offering spaces for relaxation, meditation, and emotional support, design fosters healing and minimizes the emotional burden of illness. The incorporation of art and nature elements serves as a source of inspiration and solace during challenging times. Sustainability and green design principles not only reduce the environmental footprint of healthcare facilities but also contribute to patient recovery and well-being. The future of architectural design within HSCT units and hematology departments is marked by emerging trends that emphasize patient-centricity, wellness, and the integration of technology and telemedicine. The achievements and future prospects outlined in this manuscript underscore the imperative of collaboration among healthcare professionals, architects, and designers. This collective endeavor transcends disciplinary boundaries and unites stakeholders in the common pursuit of optimal patient care. Healthcare professionals bring their expertise in clinical care and patient needs, architects contribute their knowledge of design principles and functionality, and designers infuse creativity and aesthetics into healthcare environments. Together, they form a synergistic alliance that has the potential to reshape the landscape of healthcare delivery.

As we stand at the precipice of a new era in healthcare architecture, we are presented with a profound opportunity. By prioritizing the architectural aspects of our medical facilities, we have the potential to create environments that foster improved patient experiences and successful hematopoietic cell transplantations.

This paper aims to serve as a testament to the transformative power of architectural design within HSCT units and hematology departments. It is a call to action for healthcare organizations, architects, designers, and policymakers to recognize the pivotal role of design in healthcare and to prioritize the creation of environments that support the well-being of all those touched by the intricate journey of hematopoietic cell transplantation. In conclusion, architectural design is not a passive backdrop to healthcare but an active participant in the journey towards better patient outcomes, enhanced healthcare quality, and environmental sustainability. As we continue to advance in the field of healthcare, let us not overlook the critical role that design plays in shaping the future of HSCT care and the broader landscape of healthcare delivery.

Conflict of interest statement

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Evaluation of diastolic wall strain in patients with mitral valve regurgitation

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Abstract

Aim: Diastolic wall strain (DWS) is a noninvasive, easy, echocardiographic parameter that has been used to determine left ventricular diastolic stiffness. The relationship between left ventricle functions and diastolic wall strain is previously revealed but we don't know if this method correlates with mitral regurgitation (MR) severity or not. In this study, we sought to determine the relationship between DWS and MR.

Methods: This study included 107 subjects with primary mitral regurgitation, divided in two groups as mild-to-moderate and severe mitral regurgitation, and 54 control subjects. We calculated the DWS from the M-mode echocardiographic measurements of the LV posterior wall thickness at end-systole and end-diastole during sinus rhythm.

Results: MR group had lower values of DWS than control subjects and severe MR group had the lowest ones (0.38 ± 0.06; 0.27 ± 0.07; 0.15 ± 0.035 respectively and p <0.001). DWS was negatively correlated with the disease severity and had the largest size effect (r: -0.851 p<0.001, $\eta_p^2 = 0.701$).

Conclusions: DWS is a qualitative and easy method. It could be used for determining the severity of MR

Keywords: *Diastolic wall strain; left ventricular diastolic stiffness, mitral regurgitation, primary mitral regurgitation*

1. Introduction

The incidence of valve diseases increases with age. The prevalence is under 2% in the ages before 65 and it is 13.2% after the age of 75.[1] Increased prevalence of valve diseases with age is together with the changes in the etiology. Especially in developed countries degenerative causes are the first reason while rheumatic valve diseases are still common in developing countries.

Mitral regurgitation (MR) and multiple valve involvement are the most common valve diseases in our country.[2] MR can be primary (organic) or secondary (functional). Primary MR develops as a result of anatomical disorder of mitral apparatus and numerous anatomical lesion may cause this. Secondary or functional regurgitation is almost due to myocardial diseases and mitral valves are structural as normal.[3-4]

MR can be asymptomatic for a long time. When LV function is impaired symptoms may occur, most commonly seen as exertional dyspnea. Also orthopnea, paroxysmal nocturnal dyspnea, fatigue as a result of reduced cardiac output and decreased exercise capacity can be seen.[5]

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Echocardiography is the gold standard in diagnosis. Grading of MR is complex and difficult. Doppler echocardiography with clinical examination is the most important method in diagnosis. Rating of MR jet with eye- only results in error and is not recommended. Quantitative parameters such as vena contract width, regurgitant orifice area, insufficiency volume and fraction have prognostic significance and are recommended for patients with MR.[6] However, it is not always possible to use these quantitative parameters in daily practice in clinics where there are few patients. Also, differences in measurement between clinicians limit their usability.

LV diastolic wall strain (DWS) is an echocardiographic index which gives information about LV stiffness in preserved LV systolic functions. It is independent of loading conditions and noninvasive.[7] There are studies showing that impaired DWS and increased LV stiffness play an important role in the pathophysiology of both preserved and low ejection fraction heart failure and are associated with the prevalence of atrial fibrillation in normal heart. [8] The possible usefulness of DWS in patients with MR has not been reported previously. The aim of our study was to investigate whether DWS could be used for classification of MR.

2. Materials and methods

One hundred sixty-one consecutive patients; 54 controls and 107 with MR; were included in the study. We excluded patients who had other severe valvular disease, end stage renal disease, stroke,

insufficient quality of echocardiography, reduced LV ejection fraction or presence of wall motion abnormalities. These patients were admitted to Meram Medical Faculty Hospital Cardiology outpatient clinic for any cardiovascular symptoms. The Meram Medical Faculty Hospital approved the study protocol and this study was performed in accordance with the Declaration of Helsinki.

Doppler, 2-dimensional, M-mode echocardiograms were acquired using standardized acquisition protocol. LV interventricular septum thickness, LV posterior wall (PW) thickness, LV end-diastolic and end-systolic dimensions were determined from M-mode and ejection fraction was calculated by the Teichholz method.

Left atrial (LA) diameter was determined from the M-mode echocardiography as the largest distance between the posterior aortic wall and posterior wall of LA at end-systole. [9] Mitral inflow velocities, peak early E and peak late A, were acquired in the apical four-chamber view. DWS was calculated using the formula: LV DWS = (LVPWs - LVPWd) / LVPWs,, where LVPWs is the LVPW thickness at end-systole and LVPWd is the LVPW thickness at end-diastole using M-mode (figure 1).[10] In patients with MR detected by color doppler echocardiography, two different cardiologists performed visual grading and patients were grouped as mild or moderate and severe MR.

2.1. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as count and percentage. Oneway Anova test was used for analysis of continuous variables, and the difference between nominal variables were compared with chi-square testing. Multiple comparisons of the means of variables were performed using the LSD post hoc test. A multivariate analysis was used to adjust for the clinical and echocardiographic variables potentially affecting the MR classification and partial eta squared (η_p^2) was used to n-measure the effect size of these variables. Statistical significance was accepted at <0,05. Statistical analysis were performed with the SPSS version 16 (SPSS, Chicago, IL, USA).

3. Results

Table 1 shows clinical and demographic characteristics of the study cohort. There were no differences in age, gender, prevalence of diabetes mellitus, hypertension, hyperlipidemia, family history of heart disease and smoking between the 3 groups. However, the prevalence of atrial fibrillation was higher in MR group as expected and the difference was statistically significant (p<0.001).

Table 2 shows echocardiographic data. Patients in 3 groups had a similar LV systolic function assessed by LV ejection fraction. LV end-diastolic, end-systolic diameters and left atrial diameter were larger in MR group and correlated with the severity. There was an increase in posterior wall end diastolic thickness with severity of MR while LV posterior wall end systolic thickness decreased. When the doppler echocardiographic indices representing LV diastolic function were compared, both E/E' septal and E/E' lateral were higher in MR group and E/A was lower in MR, the difference was statistically significant in all parameters. Although, echocardiographic measurements showed significant differences among three groups, the effect size of DWS was higher than the other parameters (p<0.001, η_p^2= 0.701). DWS correlated well with E' septal , E' lateral , E/E' septal and E/E' lateral values and LA diameter (p=0.004 R= 0.228, p<0.001 R=0.275, p<0.001 R= -0.369, p<0.001 R= -0.380, p<0.001 R=-0.655 respectively). We could not find any correlation between E/A and DWS (p=0.097).

MR severity did not correlate with comorbidities like systolic and diastolic blood pressure values, hypertension, diabetes mellitus, dislipidemia, smoking or family history. There was a weak significant correlation between most echocardiographic parameters except LV ejection fraction and mitral inflow E/A ratio and MR. The strongest correlation was between MR and LV DWS (r = -0.851, p <0.001) (Table 3). DWS decreased as MR severity increased.

Table 1

Basic demographic and clinical data according to study groups

Variables	Control group (n=54)	Mild-moderate MR group (n=53)	Severe MR group (n=54)	P
Age, years	60 ± 9	57 ± 10	56 ± 10	0.448
Female, n (%)	35 (65)	37 (70)	30 (56)	0.299
Hypertension, n (%)	30 (56)	31 (58)	29 (54)	0.881
Systolic Blood Pressure, mm Hg	123 ± 15	126 ± 14	120 ± 12	0.153
Diastolic Blood Pressure, mm Hg	74 ± 9	75 ± 10	74 ± 9	0.892
Diyabetes Mellitus, n (%)	17 (31)	15 (28)	29 (54)	0.901
Hyperlipidemia, n (%)	15 (54)	11 (21)	14 (26)	0.685
Family history, n (%)	20 (37)	18 (34)	17 (31)	0.830
Smoking, n (%)	14 (26)	7 (13)	8 (15)	0.174
Atrial Fibrilation, n (%)	0 (0)	7 (13)	18 (33)	<0.001*

*Notes: LV, left ventricular; MR, mitral regurgitation; * The difference was statistically significant (p < 0.001).*

Table 2

LV diastolic wall strain and baseline echocardiographic measurements according to study groups

Variables	Control group (n=54)	Mild-moderate MR group (n=53)	Severe MR group (n=54)	P	η_p^2
LV diastolic diameter, mm	45.2 ± 4.5	48.2 ± 4.6	53.3 ± 5.7	<0.001*	0.307
LV systolic diameter mm	26.2 ± 3.6	28.5 ± 5.4	34.9 ± 6.7	<0.001*	0.313
LV diastolic posterior wall thickness, mm	9.4 ± 1.0	9.9 ± 1.2	10.7 ± 1.4	<0.001*	0.151
LV diastolic posterior wall thickness, mm	15.3 ± 1.7	13.7 ± 1.7	12.5 ± 1.5	<0.001*	0.323
LV ejection fraction, %	59.1 ± 7.7	60.0 ± 4.0	58.5 ± 2.7	0.328	0.009
Left atrium diameter, mm	31.59 ± 4.00	40.01 ± 6.13	58.70 ± 6.88	0.002**	0.514
E velocity, m/s	75.85±16.11	75.00 ± 17.21	95.70 ± 23.06	<0.001*	0.246
A velocity, m/s	69.14 ± 16.26	75.76± 20.27	78.62 ± 18.66	0.043**	0.065
E / A ratio	1.29 ± 0.40	1.14 ± 0.32	0.98 ± 0.26	<0.001*	0.118
E /E' (septal)	7.56 ± 2.55	10.56 ± 4.61	12.76 ± 4.32	<0.001*	0.273
E /E' (lateral)	6.53 ± 2.15	8.52 ± 3.87	11.22 ± 4.06	<0.001*	0.241
LV diastolic wall strain	0.376 ± 0.063	0.272 ± 0.069	0.148 ± 0.035	<0.001*	0.701

*Notes: LV, left ventricular; MR, mitral regurgitation. * The difference was statistically significant (p < 0.001). ** The difference was statistically significant (p < 0.05).*

Table 3

Correlation of LV diastolic wall stress with baseline demographic, clinical, and echocardiographic data in the study population

	r value	p value
Basic demographic and clinical data		
• Hypertension	-0.015	0.848
• Diabetes mellitus	-0.033	0.674
• Hyperlipidemia	-0.018	0.825
• Systolic blood pressure	-0.087	0.273
• Diastolic blood pressure	-0.015	0.848
• Smoking	-0.118	0.135
• Family history	-0.048	0.546
Echocardiographic parameters		
• Early mitral inflow velocity, E (m/s)	0.384	<0.001*
• Late mitral inflow velocity, A (m/s)	0.246	0.004**
• E/A ratio	0.134	0.121
• E/e' lateral	0.487	<0.001*
• E/e' septal	0.480	<0.001*
• LV ejection fraction (%)	0.070	0.381
• Left atrium diameter, mm	0.269	0.001*
• LV diastolic diameter, mm	0,269	0,001**
• LV systolic diameter, mm	0.544	<0.001*
• LV systolic posterior wall, mm	-0.566	<0.001*
• LV diastolic posterior wall, mm	0.382	<0.001*
• LV diastolic wall strain	-0.851	<0.001*

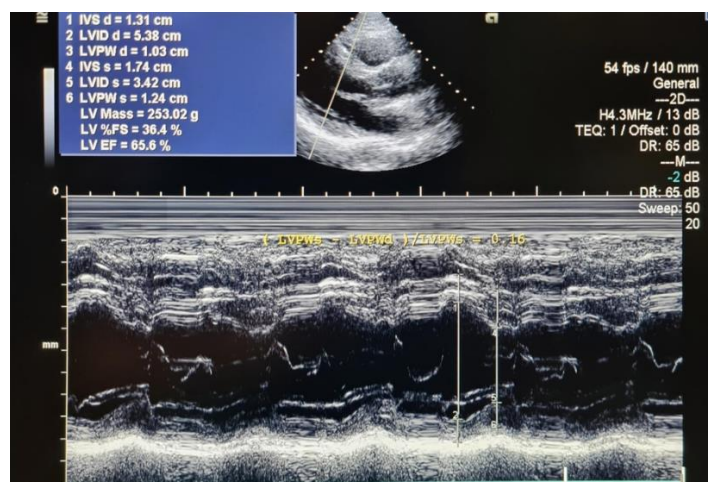
*Notes: LV, left ventricular; MR, mitral regurgitation. * The difference was statistically significant (p < 0.001). ** The difference was statistically significant (p < 0.05).*

Box plot graph of LV DWS (0.376 ± 0.063 vs. 0.272 ± 0.069 vs. 0.148 ± 0.035; p <0.001* ηp^2=0.701) values in healthy control group and patients with mild-mode MR and severe MR groups, respectively, is shown in Figure 2. LV DWS values were shown to be significantly decreased in patients with severe MR (Figure 2). DWS decreases as the severity of MR increases.

A significant correlation was found between DWS and severity of MR (r=-0.851; p<0.001) (Table 2). ROC curve analysis found that a DWS lower than 0.28 was associated with the presence of MR , with a sensitivity of 86 % and a specificity of 90 % (Area under the ROC curve=0.952; 95% CI 0.924–0.981; p<0.001) (Figure 3). ROC curve analysis found that a DWS lower than 0.2 was associated with severe MR , with a sensitivity of 95 % and a specificity of 94 % (Area under the ROC curve=0.966; 95% CI 0.939–0.993; p<0.001) (Figure 3).

Figure 1

Calculation of left ventricular diastolic (LVPWd) and systolic (LVPWs) posterior wall thickness and diastolic wall strain (DWS) by M-mode echocardiography. LV DWS = (LVPWs - LVPWd) / LVPWs



4. Discussion

To the best of our knowledge, this is the first report to investigate the usability of DWS in classification of MR. The main findings can be summarized as follows. First, we demonstrated that patients with MR had lower DWS levels than controls. Second, in severe MR the lowest DWS values were found. Third, DWS had the highest

Figure 2

Box plot graphic showing the relationship with LV diastolic wall strain in patients with mild-moderate MR, severe MR, and control subjects. Notes: MR, mitral regurgitation; LV, left ventricular.

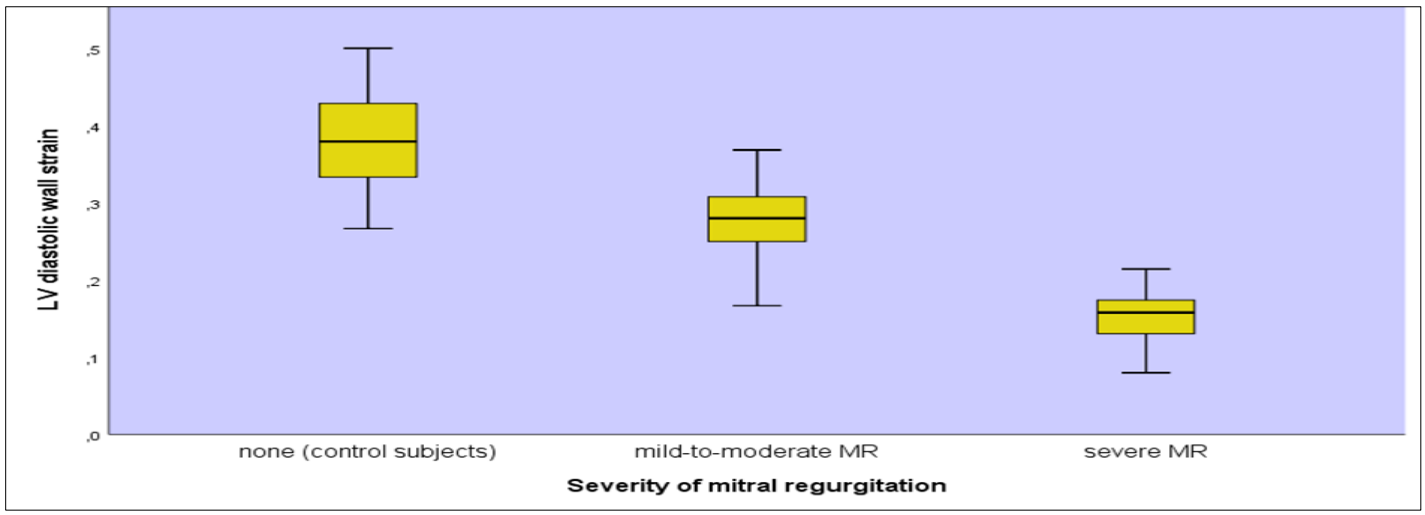
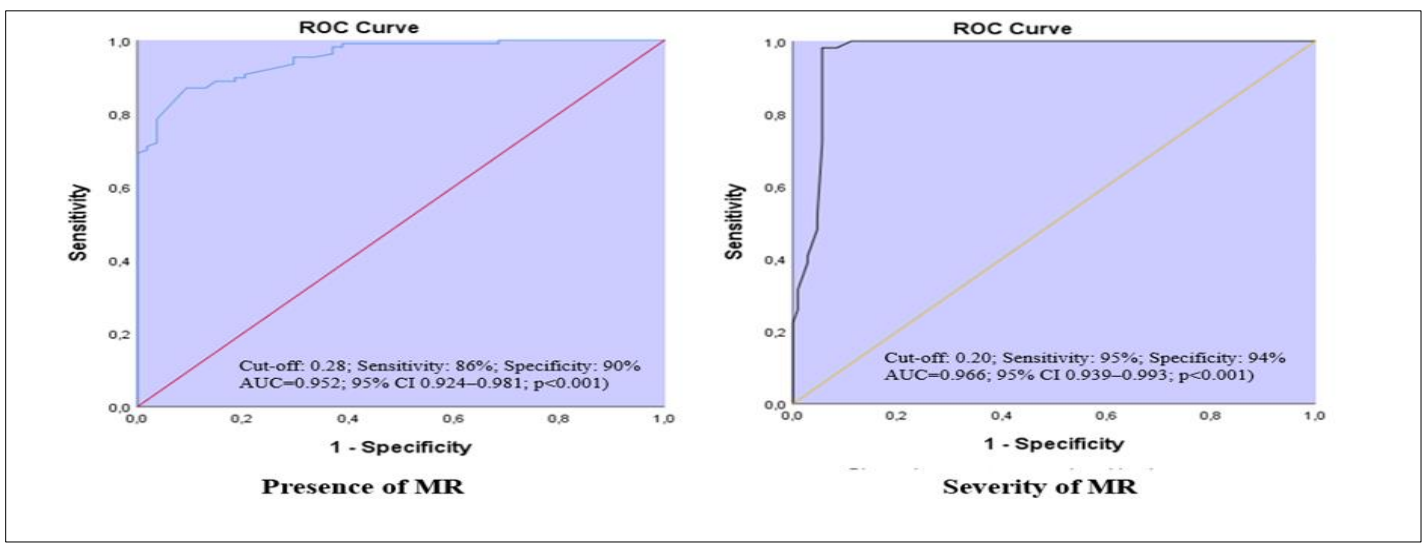


Figure 3

ROC curve analysis showing the relationship of left ventricular DWS to the presence and severity of MR. Notes: MR, mitral regurgitation; LV, left ventricular.



effect size on classification of MR and the best correlation coefficient with MR. These findings suggest that DWS, an easy measurement from 2-D transthoracic echocardiography, may be used for determining MR severity.

Takeda et al. reported that DWS is an easy and noninvasive echocardiographic measurement that indicates increased LV stiffness and correlates well with invasive methods in animal models.[11] Lower DWS values predict subtle diastolic dysfunction in preserved ejection fraction heart failure and have poor prognosis. There have been no studies using DWS value for classification of patients with MR.

LV diastolic dysfunction is common and relevant with the heart failure and increased mortality. MR negatively affects the relaxation of the LV. On account of this, quantitation of MR is more important for clinicians and evaluating MR patients include multidisciplinary approach like symptoms, exercise capacity, echocardiographic measurements and arrhythmia risk. MR constitutes a volume load on LV and increases afterload directing the LV to decompensation. LV stiffness increased and diastolic dysfunction occurs firstly. Echocardiographic measurements, which are used to evaluate MR in daily practice, are performed on 2-dimensional, continue waves doppler, pulse waves doppler and color doppler echocardiography. Some of them are quantitative and some are qualitative. The measurements in these two groups should be used together when deciding on the severity of MR.

In our study, the strain average of the control group was 37 %, the strain average of patients with mild-to-moderate MR was 26 %, and the strain average of patients with severe MR was 14 %. Strain cut value for MR is 0.20; 95% sensitivity and 94% specificity. The measured strain value was found to be effective in high range without

predicting the intensity of MR. There is a negative correlation between MR grade and diastolic strain and a decrease in the amount of residual cardiac strain in MR severity. Based on our analysis, we found that DWS was correlated well with tissue E' velocity and E/e' ratio. Nagueh et. al showed that the e' velocity measured with tissue Doppler echocardiography is sensitive for abnormal LV relaxation.[12] Takagi and colleagues reported that lower DWS was associated with increased LV stiffness and correlated with E/E' [13] and Ohtani et. al have confirmed the correlation between DWS and tissue doppler E' velocity. These previous studies encourage our findings. As a result, posterior DWS is as effective and simpler as the new clinical and echocardiographic parameters. The relationship between 3 groups and DWS is shown in Figure 2. DWS decreases as the severity of mitral regurgitation increases.

Our study has few limitations. First, this is a single center and a small group of participants study. Second, strain was only measured from 2-dimensional transthoracic echocardiography. Futrhermore, the patients with MR were grouped by only using qualitative methods.

5. Conclusion

DWS, easily calculated from 2-dimensional echocardiography, correlates well with other echocardiographic parameters and could be a determinator for MR classification. Further prospective larger group studies are needed.

Statement of ethics

The present study protocol was reviewed and approved by Meram Medical Faculty Hospital Ethics Committee ((56-2017)).

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of interest statement

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding, and similar situations in any firm. Mert Evlice[2], MD; İbrahim Halil Kurt[2], MD;

Availability of data and materials

The data supporting this study's findings are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Idea/Concept/Design: Mükremin Coşkun[1, 2], MD; Mehmet Akif Düzenli[1], MD; Control/Supervision: Mert Evlice[2], MD; Mehmet Akif Düzenli[1], MD; Data Collection and/or Processing: Mükremin Coşkun[1, 2], MD; Mehmet Akif Düzenli[1], MD; Analysis and/or Interpretation: Mükremin Coşkun[1, 2], MD; Mehmet Akif Düzenli[1], MD; Mert Evlice[2], MD; Literature Review: Mükremin Coşkun[1, 2], MD; Mert Evlice[2], MD; İbrahim Halil Kurt[2], MD; Mehmet Akif Düzenli[1], MD; Writing the Article: Mükremin Coşkun[1, 2], MD; Mert Evlice[2], MD; Critical Review: Mert Evlice[2], MD; İbrahim Halil Kurt[2], MD; References: Mert Evlice[2], MD; Mükremin Coşkun[1, 2], MD; Materials: Mükremin Coşkun[1, 2], MD;

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Effects of Curcumin and Doxorubicin on the Viability of Neuroblastoma Cancer Cell Line

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Abstract

Aim: Neuroblastoma (NLB) has a very important place among childhood diseases, and despite all the methods used in treatment, it is very difficult to prevent neuroblastoma invasion. The number of studies showing that curcumin, the most active component of turmeric, is not toxic, is increasing day by day. In this study, the anti-cancer activities of curcumin (Cur), one of the important active compounds, were demonstrated in the human neuroblastoma cancer cell line (Na2B).

Methods: NA2B was used in the study. To determine the IC50 doses of doxorubicine (Dox) and Cur, NA2B cells line were cultivated with an automatic pipette. 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) analysis was performed to analyze cell survival (viability). Inhibition levels in the cells were determined at 24 and 48 hours.

Results: While the IC50 of NA2B cell proliferation was approximately 124.5 uM at the 48th hour in Dox-treated cells, the IC50 value of Cur at the 48th hour was found to be 224.6 uM.

Conclusions: These results showed that Cur could be an alternative agent in the treatment of neuroblastoma, and its fewer side effects compared to other chemotherapeutic agents such as Dox would increase its preferability.

Keywords: *Neuroblastoma, NA2B cell line, cancer, MTT, curcumin*

1. Introduction

Neuroblastoma is the most common extracranial solid tumor in children. It constitutes 7-10% of pediatric tumors.[1] NBL, which is common from the neonatal period onwards, has a good prognosis in the early stages and in those younger than one year of age, but is a cause of mortality in older children and in the metastatic stage. It is important to recognize the epidemiological and clinical features of neuroblastic tumors, which are common and present different clinical features.

Curcumin is also known as an anti-inflammatory and an agent that reduces the effect of chemicals taken in chemotherapy.[2] Cur has many properties and shows a high anti-proliferative effect, resulting from its interaction with various molecules such as growth factors, enzymes, carrier proteins, metal ions, tumor suppressors, transcription factors, oncoproteins and nucleic acids. Thus, many studies have shown that it is beneficial against breast, cervical and melanoma cancers, such as effective induction of apoptosis.[3]

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We can also say that curcumin's low toxicity towards normal cells and tissues has attracted much attention in cancer treatment Recent studies on curcumin have revealed that this compound has poor bioavailability, hydrophobicity, poor cellular uptake and rapid metabolism.[4] To eliminate this problem, experts have conducted various experiments, many of which perform nano carriers. Additionally, curcumin affects different signaling pathways and molecular targets involved in the development of various cancers.[5] Cur has been shown to have therapeutic benefits in multiple chronic diseases.[6] In particular, inflammation, arthritis, metabolic syndrome, liver disease, obesity, neurodegenerative diseases and most importantly, cancer. There are not many alternative treatment options for cancer cases other than chemotherapy. This study aimed to reveal the effectiveness of curcumin as an alternative treatment on cancer cell invasion and migration.

Medicinal plants are very important in pharmacological research and development of drugs. The type and development of cancer is important in the fight against cancer, because many properties of different types of cells come into play and treatment with a single therapy is rarely possible.[7] At this point, combination treatments have come into play and new combination treatments are being developed every day. In combinations, targeted different pathways and preferred chemotherapy agents are reduced to lower doses and toxicity is significantly reduced.[8,9] Significant side effects occur in

patients due to the fact that the drugs are chemically synthesized. In order to overcome this problem, the discovery and development of new active substances derived from natural products has become the main focus of research.[10,11] In this study, the anticancer effects of curcumin, which can affect the neuroblastoma cell line, which is a childhood cancer, can be an alternative treatment, and has been reported in many studies to have fewer side effects, were investigated.

2. Materials and methods

2.1. Cell culture

NA2B neuroblastoma cells were purchased from American Type Culture Collection (ATCC, Manuassas, VA). NA2B cell line; It was incubated in appropriate medium (DMEM; Dulbecco's modified Eagle's medium) containing 10% fetal bovine serum (FBS) and 1% antibiotics (Penicillin, Streptomycin) and in an environment of 37°C and 5% CO_2. The culture medium was changed every 24 hours until the cells reached the required majority.[12]

2.2. Cell Viability Test (MTT assay)

To determine the IC_{50} doses of Dox and Cur, Na2B cells were seeded in 96-well plates at 3000-5000/well/cell. At the end of one night, 10-1000 nM doses of Dox and 10-1000 µM doses of Cur were applied in 9 different concentrations with serial dilution and incubated for 24 and 48 hours. The MTT test is a method that determines cell proliferation and viability by reducing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to the formazan product. While performing the MTT test, all procedures were performed in as little light as possible. On the first day, Na2B cells were incubated for 24 hours, with 16,000 cells added to each well, making a total volume of 300 µL. The same experiment was repeated after inducing toxicity with Dox for 24 h and adding negative control concentrations. On the second day, cells were incubated in proliferation medium. Cur containing medium was then removed and 10 µL of MTT stock solution was added, and the cells were incubated at 37°C for 4 h. After pipetting the MTT solution, DMSO was added and left at room temperature for 10 minutes. A microplate reader spectrophotometer with a wavelength selection system was used to determine the absorbance at 570-690 nm. The absorbances measured compared to the control group after three replicates were used to determine the protective effect of Cur.[13]

2.3. Statistical analysis

Statistical analyzes were performed with SPSS 20.0 software (IBM, USA) and are presented with standard error bars in the graphs. Analysis results were made with one-way ANOVA and Tukey's multiple comparative test.

3. Results

The antiproliferation effects of Cur and Dox against the NA2B cell cell line are shown in Table 1 and Table 2.

At the end of 24 hours of treatment of 250 nM Dox concentration, cytotoxic activity and 86.6% cell viability were obtained in the NA2B cell line. However, the highest cytotoxic activity of the same 24-hour Dox application was obtained with a cell viability of 57.4 at a concentration of 1000 nM. Additionally, IC_{50} could not be found in 24-hour Dox application. After 48 hours of Dox application, IC_{50} was determined as 124.5 nM. The highest 48-hour Dox toxicity was obtained at 750 nM and 1000 nM concentrations, respectively, with 33.4% and 8.2% cell viability (Figure 1, Table 1). 250 µM Cur concentration for 24 hours, the highest cytotoxic activity and cell viability of 70.4% were obtained in the NA2B cell line. IC_{50} could not be determined in 24-hour Cur application. After 48 hours of Cur application, IC_{50} was determined as 224.6 µM. The highest 48-hour Cur toxicity was 16.8% and 18.4% cell viability at 750 nM and 1000 nM concentrations, respectively (Figure 2, Table 2).

Table 1

Cell viability obtained from 24 and 48 hours of Dox application in NA2B cell line at 9 different concentrations obtained as a result of serial dilution in the concentration range of 0.5-50 µM.

NA2B-Dox		N	Cell viability (%)	Std.Dev.	Std. Err.
S24h	,00	6	100,00	5,40	1,70
	10,00	6	96,21	2,92	1,70
	25,00	6	98,56	5,79	2,27
	50,00	6	94,51	4,05	1,45
	75,00	6	96,33	3,22	1,33
	100,00	6	94,26	2,84	1,12
	250,00	6	86,65	4,23	1,73
	500,00	6	68,47	1,67	0,62
	750,00	6	62,34	2,75	1,43
	1000,00	6	54,75	1,34	0,21
S48h	,00	6	100,00	5,47	2,34
	10,00	6	78,45	4,29	1,47
	25,00	6	76,76	2,52	0,89
	50,00	6	76,20	2,53	1,13
	75,00	6	78,13	3,73	2,24
	100,00	6	53,95	1,20	0,29
	250,00	6	19,09	1,14	0,46
	500,00	6	10,78	0,64	0,34
	750,00	6	11,21	0,37	0,11
	1000,00	6	8,51	0,77	0,26

Figure 1

% Cell viability compared to the vehicle control group after 24 and 48 hours of Dox application.

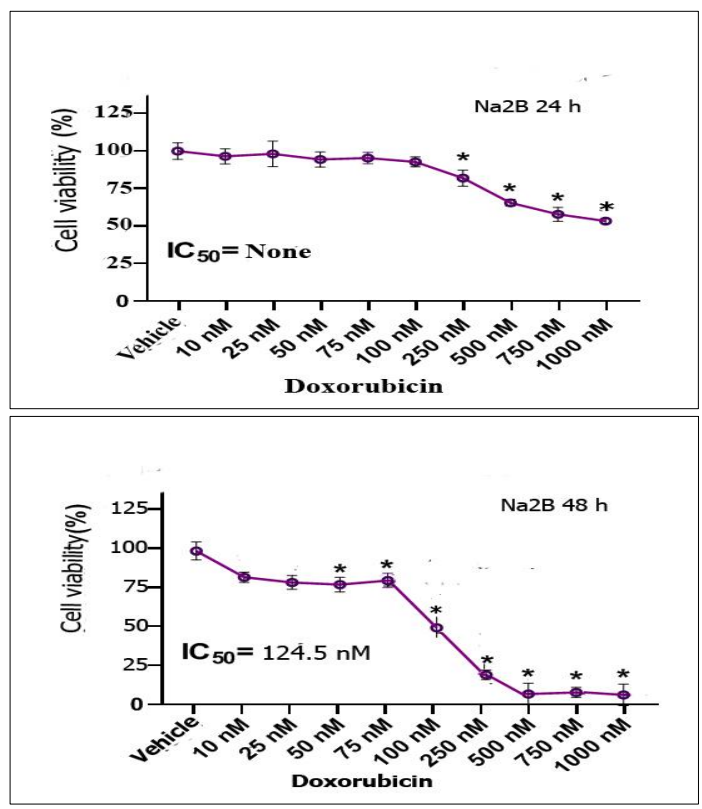


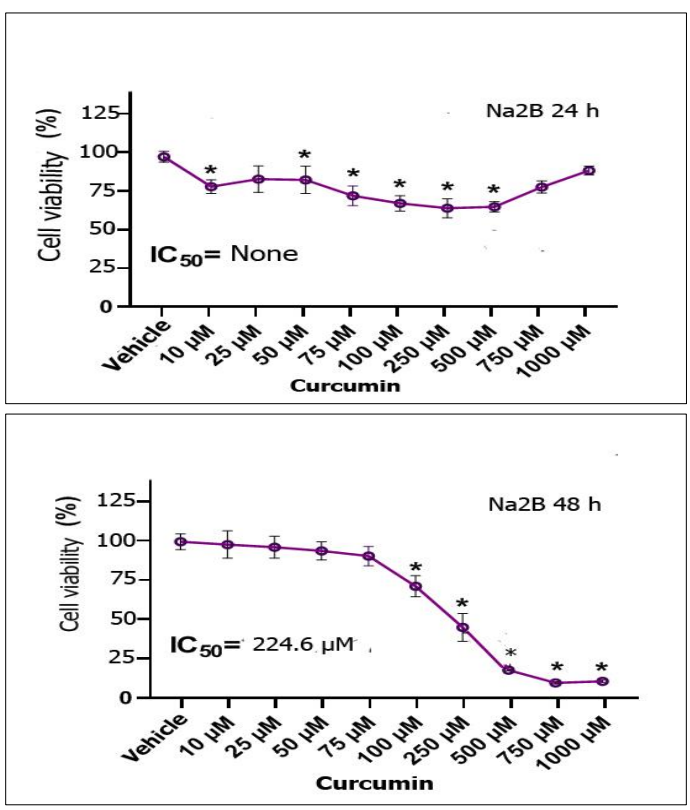
Table 2

Cell viability obtained from 24 and 48 hours of Cur application in 9 different concentrations obtained as a result of serial dilution in the NA2B cell line in the concentration range of 0.5-50 µM.

NA2B-Cur		N	Cell viability (%)	Std.Dev.	Std. Err.
S24h	,00	6	100,00	4,40	1,70
	10,00	6	76,41	3,92	1,68
	25,00	6	78,65	3,79	2,12
	50,00	6	79,43	2,05	1,23
	75,00	6	75,33	2,22	1,33
	100,00	6	74,26	2,64	1,21
	250,00	6	73,65	5,23	1,63
	500,00	6	74,47	1,87	0,42
	750,00	6	77,34	2,25	1,37
	1000,00	6	80,73	1,64	0,22
S48h	,00	6	100,00	4,47	1,34
	10,00	6	94,24	2,29	1,57
	25,00	6	89,66	3,52	0,24
	50,00	6	86,46	3,53	1,13
	75,00	6	84,41	3,43	2,25
	100,00	6	73,85	2,20	0,24
	250,00	6	44,19	1,24	0,32
	500,00	6	16,75	0,35	0,33
	750,00	6	8,43	0,33	0,13
	1000,00	6	11,41	0,57	0,24

Figure 1

% Cell viability compared to the vehicle control group after 24 and 48 hours of Cur application.



4. Discussion

In this study, we showed that curcumin and doxorubicin prevent the proliferation of neuroblastoma NA2B cells and exert this effect by suppressing cell viability. With these results, we found that curcumin, a natural phenolic compound, plays protective roles in highly metastatic cancer types such as neuroblastoma and its antioxidant potential can be benefited by using it in combination with chemotherapeutics used in treatment. Neuroblastoma is a complex disease that affects the sympathetic nervous system.[14] Most of the mortalities associated with neuroblastoma occur due to metastasis to lymph nodes and bones.[15] Therefore, preventing cancer cell invasion and migration is an important step to prevent metastasis. Neuroblastoma cell invasiveness and metastasis depend on the ability of tumor cells to break down the extracellular matrix to detach from the primary tumor and enter the bloodstream or lymphatic system, then travel to distant sites and reattach.[16] Phenolic compounds have been shown to suppress MMP2 and MMP9 levels in vascular endothelial cells, thus It has been reported that it has a protective effect against degenerative diseases.[17]

The anti-oxidant effects of natural phenolic compounds have been determined by many studies. With their radical scavenging effects, phenolic compounds also reduce the risk of cancer formation. In an in vitro study, the antioxidant activity of curcumin was determined.[18] In addition to the primary antioxidant effects of these compounds, it was also determined that they had a broad-spectrum biological effect on carcinogenesis.[19] Studies on this subject show that phenolic compounds, especially polyphenols, prevent the formation of cancer.[20] Studies have shown that compounds are effective on tumor cell growth and proliferation.[21,22] It has been determined that natural compounds with phenolic structures have an anti-proliferative effect on human tumor cell lines. It has been stated that the anti-proliferative activities and therefore the potential anti-cancer effects of phenolic compounds originate from their aromatic rings and hydroxylic groups.[23] In one of the studies conducted with curcumin, the anticancer properties of nanocurcumin and its anticancer effects with nanocarriers in different types of cancer were investigated.[24] It has been shown that curcumin nanoformulation can affect cellular pathways effective in differentiation and cell proliferation.[25] Particularly from in vivo studies, they reported that in the tumor model with BALB/c mice, the existing tumor size was reduced more effectively and efficiently when nano-curcumin was applied to the mice.[26] In an in vitro study conducted on neuroblastoma cells, it was determined that curcumin had significant effects on cell viability. In our study, it was determined that curcumin had an anti-proliferative effect on the neuroblastoma cell line. In this study, we found that curcumin reduced the proliferation of Na2B cells, similar to the effects of previous phenolic compounds. Although plant phenolic compounds have been shown to be effective on tumor growth and cell proliferation, more experimental studies are needed on this subject due to the mortality of cancer disease and deficiencies in treatment.

5. Conclusion

The current study shows that Cur may be a promising treatment option for the treatment of neuroblastoma cancer and an alternative to commonly used chemotherapy treatment. More and comprehensive studies involving cell culture and animal models are needed regarding the effectiveness of Cur in treatment.

Statement of ethics

Ethical approval is not required because commercially available cell lines are used as an in vitro study.

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Comparison of Three Methods of Greater Trochanter Fixation in Intertrochanteric Femur Fractures (AO Type 31/A2) Treated with Cementless Bipolar Hemiarthroplasty

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Abstract

Aim: The aim of this study was to compare the three most commonly used fixation methods for the fractured trochanter major fragment in patients undergoing uncemented bipolar hemiarthroplasty for unstable intertrochanteric fractures.

Methods: The medical records of 231 acute hip fracture cases aged 65 years and older with AO classification 31/A2.2 and 31/A2.3 who underwent unilateral primary cementless bipolar hemiarthroplasty at Adana Şehir Training and Research Hospital between January 2021 and January 2023 were retrospectively analyzed. The files were classified into three groups based on the fixation technique used in the operation.

Results: There were 231 files, with a mean age of 82.3±7.9. The majority (55.8%) were classified as ASA III. The analysis resulted in no significant differences between the groups in terms of age, number of days between the day of the injury and the day of the surgery, fixation failure, nonunion, number of revision surgeries, hospitalization duration, and HHS recorded at the third and sixth-month follow-up visits. Among the 73 males and 158 females, the ratio of the side in which the fracture occurred showed no difference (p=0.854). The female rate was significantly higher in group 3 compared to other groups (p=0.003). Regarding union success, cases in group 1 had significantly lower trochanter major union rates (p<0.001).

Conclusions: This study demonstrated that in patients treated with cementless bipolar hemiarthroplasty for unstable intertrochanteric fractures, union rates were significantly higher when fixated using trochanteric grip plates.

Keywords: *Hip, intertrochanteric fracture, hemiarthroplasty, cementless stem, greater trochanter, fracture fixation, bone plates, cable*

1. Introduction

In recent years, with the increase in life expectancy, the elderly population has increased, which has significantly elevated the occurance of intertrochanteric femoral fractures. Especially, patients with unstable fragmented hip fractures have high complication and mortality rates due to their high average age, multiple underlying comorbidities, osteoporosis, impaired muscle strength and proprioceptive function, and more difficulty in rehabilitation.[1] For these reasons, the most critical factor in fracture treatment is to ensure the stability of the bone to improve healing using the most appropriate surgical procedures. Unlike femoral neck fractures, intertrochanteric femoral fractures are located in the metaphyseal region and have higher union rates. Bone fusion using a dynamic hip screw (DHS) and proximal femoral intramedullary nail (PFN) is recommended as the routine fixation procedure for this particular class of fractures.[2] Nevertheless, in the aged population who have osteoporosis and thus present with poor bone strength, complications such as shifting of the varus and femoral head cut-out are not uncommon after osteosynthesis. These patients have difficulty in weight bearing in the early period, resulting in prolonged treatment duration, elevated number and types of systemic problems, leading to poor functional recovery and health-related findings. Moreover, prolonged immobilization with multiple underlying comorbidities may worsen medical and psychiatric problems.[3] Recently, bipolar hemiarthroplasty (BPHA) for early ambulation and rehabilitation in elderly patients has become an increasingly popular surgical alternative.[4]

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BPHA, when preferred for the treatment of intertrochanteric femoral fractures, involves a few technical challenges. Firstly, it may be technically difficult to adjust limb lengths due to fractures of the trochanter major and minus. Secondly, initial fixation may be difficult due to fragmented proximal femur fractures. Finally, the reduction and the fixation of trochanteric fragments, the surfaces allocated for the connection for the iliopsoas and abductor muscles, become difficult due to the scattered characteristics of the fracture. However, reduction and fixation of the afore-mentioned pieces require completion because stable fixation, especially of the greater trochanteric fragment, plays a very important role in complete union, functional recovery of the hip joint, and prevention of postoperative prosthetic dislocation.[5]

Various internal fixation materials are presented, and fixation procedures are described to provide stable fixation and bone healing of the fractured fragment in the trochanter major, including tension band wiring, short or long trochanteric grip/periprosthetic cable plates, titanium cables, multifilament polymer cables, and cerclage wires.[6–9] However, implant failure and nonunion rates of up to 50% have been reported.[6]

After the BPHA procedure performed for fragmented, unstable intertrochanteric fractures, nonunion of the fractured trochanter major fragment resulting in decreased hip abductor strength causes pain in the trochanteric region, gait disturbances, and prosthesis dislocation. Therefore, structural reduction and a firm fixation of the fractured trochanter major fragment is preferred by more surgeons, but the choice of fixation method is still controversial.[10]

In this study, we compared the three increasingly being preferred fixation procedures used for the fractured trochanter major fragment in patients undergoing uncemented BPHA for unstable intertrochanteric fractures.

2. Materials and methods

2.1. Study Design and Data Collection

The medical records of 683 acute hip fracture cases aged 65 and older who underwent unilateral primary cementless bipolar hemiarthroplasty surgery were analyzed between January 2021 and January 2023. The patients with 31/A2.2 and 31/A2.3 type fractures, based on the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification, were included for analysis (n=326). The number of patients lost in the six months of follow-up after the surgery was 95, and therefore, the analysis was conducted on the data of the remaining 231 files (73 males and 158 females). Age, gender, in which the hip fracture occurred, the duration between the occurrence of the hip fracture and the day of the surgery, the number of days of hospitalization, American Society of Anesthesiologists Classification (ASA) scores, the method of anesthesia, the method of fixation of the greater trochanter, the union rates of the fixated fragment, the existence of fixation failure, and Harris Hip scores (HHS) recorded at the follow-up visits conducted at the 3rd and 6th postoperative months were analyzed.

The radiological assessment included the AP and lateral X-ray images of the hip taken preoperatively and at the postoperative visits conducted at the end of the 3rd and 6th month.

The Harris Hip Scoring data collected at the postoperative 3rd and 6th month visits was used to assess pain, function, range of motion of the joint, and level of deformity. A maximum of 100 was used to define the best scores for functionality[11].

The files were classified into three groups based on the fixation technique used in the operation (Figure 1). Group 1 included patients who underwent fixation using only titanium or multifilament polymer cables, group 2 involved cases with short trochanteric grip plates, and finally, group 3 included cases with long trochanteric grip plates. Following grouping, the number of cases in the groups was 66, 100, and 65, respectively.

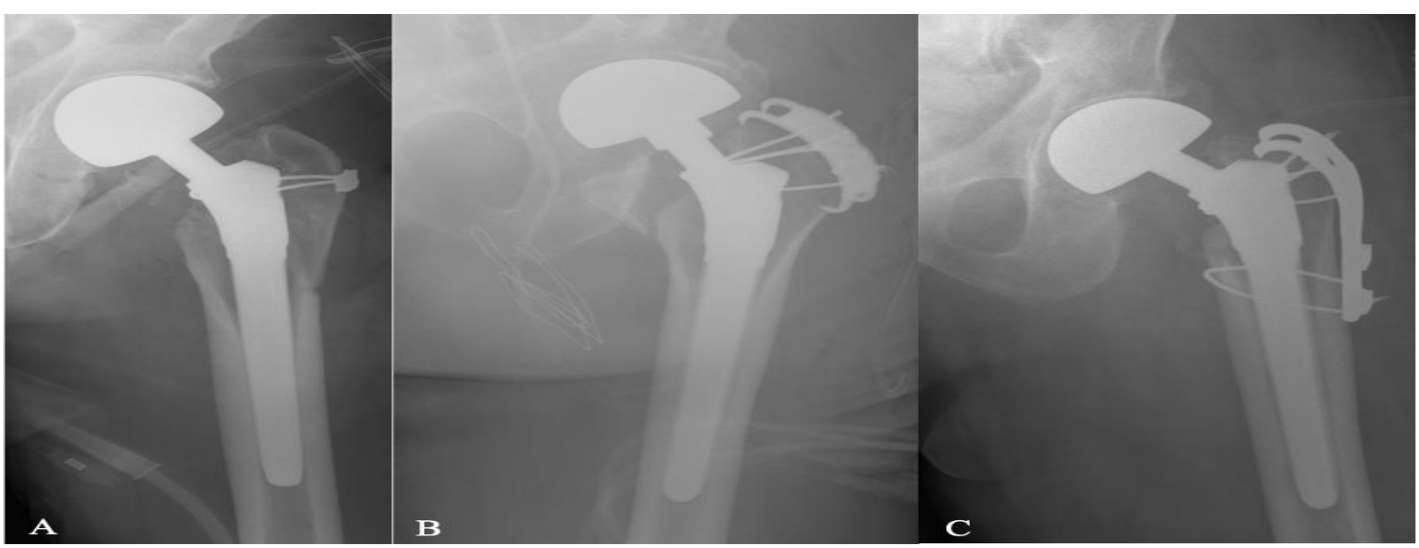
A comparative analysis of the groups was conducted, focusing on the union success of the greater trochanter fragment.

2.2 Statistical analysis

Statistical Package for the Social Sciences (SPSS) 25.0 software was used for statistical analysis of the data. Categorical assessments were abstracted as numbers and percentages, and continuous valuations were summarized as mean and standard deviation (median and minimum-maximum where necessary). The chi-square test was used to compare categorical expressions. Shapiro-Wilk test was used to assess the normality of the distribution of the collected data. The Kruskal-Wallis test was used in the analysis of more than two groups that did not show normal distribution. The statistical cut-off level for scientific meaning was considered as 0.05.

Figure 1

The methods used to fix the fractured trochanter major fragment in the study group. Group 1 (A), Group 2 (B), and Group 3 (C) are demonstrated with example radiographs



3. Results

There were 231 files, with a mean age of 82,3±7,9. The majority (55.8%) were classified as ASA III. The main features of the sampling universe are presented in Table 1.

Among the 73 males and 158 females, the ratio of the side in which the fracture occurred showed no difference (p=0.854). The female rate was considerably elevated in group 3 compared to the other two groups (p=0,003). Regarding union success, cases in group 1 had significantly lower trochanter major union rates (p<0,001) (Table 2).

The analysis resulted in no remarkable differences between the groups in the context of age, number of days between the day of the injury and the day of the surgery, fixation failure, nonunion, number of revision surgeries, hospitalization duration, and HHS recorded at the third and sixth-month follow-up visits.

Table 1

The main characteristics of the study population

		Mean	Median (Min-Max)
Age		82.3±7.9	82 (66-106)
		n	%
Gender	• Male	73	31.6
	• Female	158	68.6
The location of the fracture	• Right Hip	116	50.2
	• Left Hip	115	49.8
American Society of Anesthesiologists Classification (ASA)	• II	60	26
	• III	129	55.8
	• IV	42	18.2
Anesthesia method	• General	57	24.7
	• Spinal	174	75.3
Complications	• Trochanter major non-union	80	34.6
	• Fixation failure	27	11.7
	• Revision Surgery	14	6.1
Revision indication	Prosthesis dislocation	14	6.1
		Mean	Median (Min-Max)
Days between the injury and the surgery (day)		1.74±1.7	1 (0-10)
Hospitalization Duration (day)		5.59±4.6	4 (2-53)
Harris Hip Scores	Post-operative 3rd month	54.7±21.2	67.7 (21.2-75.85)
	Post-operative 6th month	66.8±16.7	71.65 (32.5-85.85)

Table 2

The main characteristics of the study population distributed according to groups

		Group 1 (n=66)	Group 2 (n=100)	Group 3 (n=65)	p
		Med (25-75th)			
Age		82.2 (75.8-88.3)	81 (78.3-88)	82 (76.5-87)	0.854
		n (%)	n (%)	n (%)	
Gender	• Male	27 (40.9)	36 (36)	10 (15.4)	0.003**
	• Female	39 (59.1)	64 (64)	55 (84.6)	
The location of the fracture	• Right hip	32 (48.5)	46 (46)	38 (58.5)	0.278
	• Left hip	34 (51.5)	54 (54)	27 (41.5)	
American Society of Anesthesiologists Classification (ASA)	• II	14 (21.2)	25 (25)	21 (32.3)	0.268
	• III	35 (53)	58 (58)	36 (55.4)	
	• IV	17 (25.8)	17 (17)	8 (12.3)	
Anesthesia method	• General	21 (31.8)	26 (26)	10 (15.4)	0.085
	• Spinal	45 (68.2)	74 (74)	55 (84.6)	
Trochanter major union	Achieved	26 (39.4)	79 (79)	46 (70.8)	<0.001**
Complications	• Fixation failure	10 (15.2)	8 (8)	9 (13.8)	0.305
	• Revision Surgery	1 (1.5)	9 (9)	4 (6.2)	0.141
Revision indication	Prosthesis dislocation	1	10	3	0.287
Days between the injury and the surgery (day)		2 (1-3)	1 (0.25-3)	1 (1-2)	0.506
Hospitalization duration (day)		4 (3-6)	4 (3-6)	5 (3.5-6)	0.512
Harris Hip Scores	• Post-operative 3rd month	67.7 (32.5-75.9)	67.7 (26.9-73.5)	67.7 (31.9-73.5)	0.353
	• Post-operative 6th month	71.7 (50.2-85.9)	50.5 (45.7-83.5)	73.5 (50.2-83.5)	0.068

** p<0,05, **p<0,01, †: Ki-kare, ‡: Kruskal Wallis test*

4. Discussion

In our study comparing three different fixation methods for fixation of the fractured trochanter major fragment in patients undergoing uncemented BPHA for unstable intertrochanteric fractures, we found that the union rates of the fractured trochanter major frag-

ment were significantly higher in fixation using long or short trochanteric plates.

Traditional titanium or polyethylene cables are widely used for fixation of the fractured trochanter major fragment due to the relatively simple procedure and low cost.[10] However, plates and cable systems require a larger surgical exposure than other techniques, are expensive, and trochanteric nonunion occurs more frequently.[12] Similarly, our study shows that the preference of wires and cables for fixation of the trochanter major in unstable intertrochanteric fractures undergoing cementless bipolar hemiarthroplasty results in union failure. We believe that one of the main reasons for union failure is the limited biomechanical resistance to vertical displacement and rotation. For a stable fixation, the cancellous surfaces of the fractured greater trochanteric fragment should be well compressed to resist displacing muscular forces.[13]

As emphasized by Zhu et al.[14] in their biomechanical study, the use of a trochanteric grip plate with a cable system helps to resist the multidirectional forces of the abductor's muscle in both vertical and anteroposterior planes by providing compression along the bony surface of the trochanteric fragment where the implant is placed. In parallel, we found that the union rates of the fractured trochanter major fragment were significantly higher in the groups where the fixation was provided using long and short trochanteric plates (p<0.001).

The analysis of the demographic data revealed that the mean age was 82.3±7.9 years and the number of females was significantly higher (p=0.003). The incidence of hip fracture is higher in men than in women among people under 60 years of age. Conversely, among people over 60 years of age, it is more common in women due to hormonal changes after menopause. In addition, the prevalence and incidence rates for hip fractures among women increase with age.[15]

A large study conducted by the Committee for Osteoporosis Treatment of The Japanese Orthopaedic Association, which evaluated 110,747 hip fracture cases, showed that left hips were fractured more than right hips; however, no significant difference was found between the left and right sides.[16] The analysis results did not demonstrate a substantial dissimilarity between the hip sides; the distribution was even.

In a cohort research carried out by Zaib et al.[17], which was similar in design the average age of the patients selected was 80.80±11.18 years, and 97.45% of the patients had ASA scores of 3 and above. In our study, 74.03% of the patients (n=171) had ASA scores of 3 and above, and we attributed the difference to the presence of comorbidities such as hypertensive conditions, diabetes mellitus, and ischemic heart disease, which increase with age. In our study, 74.03% of the patients (n=171) had ASA scores of 3 and above, and we attributed the difference to the presence of comorbidities such as hypertensive conditions, diabetes mellitus, and ischemic heart disease, which increase with age.

During surgery for hip fractures, spinal anesthesia is often preferred to reduce the prevalence and duration of intraoperative hypotensive episodes and potentially poor outcomes related to mortality and morbidity.[18] In our study, spinal anesthesia was preferred in the vast majority of patients (n=174, 75.3%).

Unfixed large trochanter fractures may cause impairment in the functionality of the abductor muscles of the hip joint subsequent to partial hip arthroplasty, which may generate an amplified risk of prosthesis disengagement and Trendelenburg gait pattern.[19] Zhang et al.[20], evaluated the efficacy of tension band fixation in geriatric unstable intertrochanteric fractures undergoing hip arthroplasty and reported that no cases of dislocation or fracture nonunion were observed. Besides, the HHS results were improved. In contrast, our total dislocation rate was 6.1%, the single indication for revision surgery.

Grimsrud et al.[21], in a series of 39 patients who were operated on for hip arthroplasty for unstable intertrochanteric hip fractures, one cerclage cable fixation technique was used, and the findings of the follow-up visits conducted after one year showed that all trochanters were healed and fixation failure was seen in 5 cases (12.8%). In our series, the highest rate of fixation failure among the groups occurred in group 1 (4.3%), where a similar method was used.

Ozan et al.[22] examined a total of 32 unstable trochanteric femoral fracture cases who underwent greater trochanteric fixation procedures, in which the cable method was preferred, following partial hip arthroplasty, and found nonunion in 18.7% of the cases. In our study, our total nonunion rate was 34.6%. The difference in rates might be attributed to the age of the cases; the average age of patients included in the former study was 20 years younger than ours.

In studies comparing BPHA with internal fixation for the treatment of unstable intertrochanteric fractures, it was reported that recuperation was easier and faster in the arthroplasty group due to early ambulation, adding that the frequency of pressure ulcers, pneumonia, and atelectasis was significantly lower.[23,24] The authors suggested that more favorable clinical results could be obtained with hip arthroplasty.[25] Our study assessed the mean HHS results recorded at the postoperative 6th-month follow-up visit as fair for all groups.

4.1. Limitations

Our study has several limitations. Firstly, the small sample size in the groups and the retrospective design of the study. In addition, the short follow-up period of this study is another important limitation; no long-term clinical follow-up was performed to evaluate subjective patient satisfaction.

5. Conclusion

This study demonstrated that in patients treated with cementless bipolar hemiarthroplasty for unstable intertrochanteric fractures, union rates were significantly higher when fixated using trochanteric grip plates. Despite the challenges and risks of surgery, including requiring a wider exposure and the difficulty of preserving and maintaining the hip abductor mechanism, the high union rates provide a much higher level of ambulation among the elderly population.

Statement of ethics

Ethical permission was obtained from the Adana City Training and Research Hospital Clinical / Human Research Ethics Committee for this study date on May 11, 2023, and decision number 2549 and Helsinki Declaration rules were followed to conduct this study.

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by MYG. The first draft of the manuscript was written by MYG, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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Long-Term Effects of Conventional Radiofrequency in Cases of Trigeminal Neuralgia

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Abstract

Aim: This study aimed to examine the long-term clinical and functional results of patients who underwent radiofrequency thermocoagulation (RFT) for trigeminal neuralgia (TN)

Methods: A retrospective case-control study was designed. Patients with radiofrequency thermocoagulation (RFT) for trigeminal neuralgia (TN) surgery were included. Clinical and functional outcomes of patients were examined by a visual analog scale (VAS) before the RFT and after the 15th day, 6th months 1 year,2 years and 4 years.

Results: 27 of the patients were female, and 6 were male in the study. In 90% of patients with primary trigeminal neuralgia, symptoms appear after the age of 40, with the most common age range being 40-70 years. In our series,27 patients had mandibular nerve involvement, and 6 had maxillary nerve involvement. The high pain scores in the pre-treatment (Pre-op) period (ranging from 7 to 10) decreased significantly in the post-treatment periods (15th day, 6 months, 1 year, 2 years, 4 years). In the analysis conducted with the Wilcoxon test, a significant difference was found between pre-op and all post-treatment periods.

Conclusions: Conventional RF thermocoagulation is a preferred method in the treatment of TN and among other percutaneous interventional and surgical treatment options due to its selective lesion formation, minimally invasive nature, high success rate, low complication rate and low cost. Our study includes long-term data that can confirm this result.

Keywords: *Radiofrequency thermocoagulation, Trigeminal neuralgia*

1. Introduction

TN is defined as severe, episodic pain occurring in one or more branches of the trigeminal nerve.[1,2] Due to its long-term effect, radiofrequency thermocoagulation (RFT) is used as a first-line treatment.[3]

Although its etiology is not fully understood, studied causes include damage to trigeminal connections resulting from multiple sclerosis (MS) or lacunar infarction, demyelination of the "root entry zone" of the trigeminal nerve, and, more commonly considered among neurosurgeons, vascular compression. According to Devor et al.'s hypothesis published in 2002, myelin loss in nerve fibers creates a "short-circuit" effect between progressing light touch and pain fibers, leading to severe pain.[4]

The first choice in the treatment of classical trigeminal neuralgia patients is medical treatment. Anticonvulsants are the most commonly used medications, with carbamazepine still being the gold standard. Additionally, pregabalin and gabapentin are frequently used drugs.

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Surgical treatment is an option for Trigeminal Neuralgia that cannot be treated with medication, but there is no single method for this. Various surgical methods, such as Trigeminal Radiofrequency (RF) rhizotomy, microvascular decompression (MVD), glycerol rhizolysis, trigeminal ganglion balloon compression, and radiation-surgery, may be effective in treatment, each with its own advantages and disadvantages. Among these methods, neither RF nor MVD has been proven superior to the other.[5]

Due to its long-term effect, low side effects, and short hospitalization period, radiofrequency thermocoagulation (RFT) is preferred as the first choice among interventional treatment options.[3]

RF rhizotomy to the Gasserian ganglion involves percutaneous lesioning using a special RF needle and electrode system through the foramen ovale to the retrogasserian fibers with RF energy. This method was described by Harris and Hartel at the beginning of the century and was used by Harris in large series for alcohol injections. The first use of RF energy in the Gasserian ganglion with direct current in a large series was carried out by Kirschner. Rhizotomy with RF energy (controlled thermocoagulation) was first described by Sweet.[6]

The series forming the basis of today's treatment protocols is the 353-patient series by Sweet et al., with no mortality or morbidity.[7] Controlled thermocoagulation was applied in this series, as in Schürman et al.'s series. Surgeons entering the foramen ovale with

the aid of radiographs learned where the pain was felt using electrical stimulations. They measured the temperature with the thermometer at the electrode tip and confirmed it by cooperating with the patient at the end of the procedure. The 6-year follow-up of this 353-patient series resulted in a 22% recurrence rate, 0% mortality and morbidity, and complete paresthesia in only 6 patients.

The authors concluded that the highly myelinated A-beta fibers are more resistant to heat, therefore preserving some touch sensation. By 1997, this method had been perfected with technological advancements and existing experiences, aiming to cause the least pain during the awake procedure by shifting all ablation to the retrogasserian region.[8]. During the awake procedure, cooperating with the patient, the distribution of facial sensory loss was controlled, thereby minimizing the incidence of undesirable and bothersome dysesthesias, such as corneal sensory loss.[9]

This study aimed to examine the long-term clinical and functional results of patients who underwent radiofrequency thermocoagulation (RFT) for trigeminal neuralgia (TN)

2. Materials And Methods

The ethics committee approval was obtained on June 26, 2024, with decision number 59 from Adana City Hospital. We examined 33 patients who underwent conventional RF with a diagnosis of trigeminal neuralgia at the Algology Clinic of Adana Numune Training and Research Hospital between May 2016 and December 2017. The 6-year follow-up results are presented in figure 1.

Inclusion Criteria:

- *Primary trigeminal neuralgia*
- *Ineffectiveness of medication treatment*
- *Pain visual analog scale (VAS) score above 7/10*
- *Absence of accompanying secondary disorders that could explain the symptoms*
- *Normal brain magnetic resonance imaging findings*
- *No previous interventional treatment*

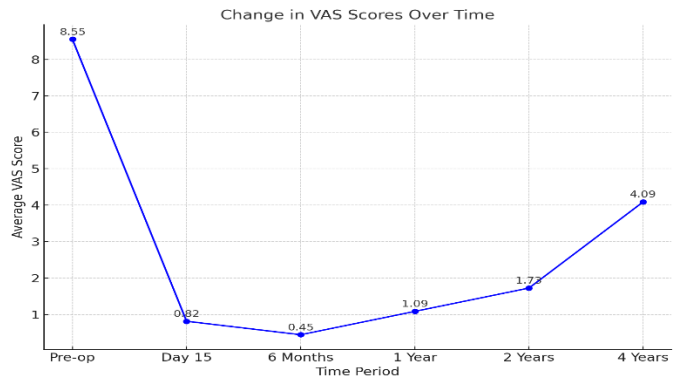
2.1. Procedure Technique

The procedure is performed under operating room conditions and radiological imaging guidance. The patient is placed in the supine position, an IV line is established, and monitoring is initiated. After local field cleaning and sterile draping, optimal imaging is achieved using C-arm fluoroscopy with an ipsilateral 15° oblique and 30° caudal angle. A 22-gauge, 100 mm RF needle with a 5 mm active tip is directed towards the foramen ovale, and the tunnel view is checked. Once the needle enters the foramen, the C-arm is positioned laterally, and the depth is checked. Sensory and motor responses are tested after appropriate positioning relative to the Gasserian ganglion.

Sensory stimulation is performed with a frequency of 50 Hz, a duration of 1 ms, and stimulation varying between 0.2 and 1 V, while motor stimulation is performed with a frequency of 2 Hz, a duration of 1 ms, and stimulation varying between 0.5 and 1.5 V. Cooperation with the patient is crucial. The patient is expected to feel sensations such as tickling, itching, and electrical sensations along the trigeminal tract corresponding to the pain. Additionally, the masseter function and ciliary reflex may be observed. Ablation is applied at 65°C, 70°C, 75°C, and 80°C for 1 minute each, for a total of 4 minutes. Due to severe pain during the ablation process, 1 mg/kg propofol and 50 micrograms of fentanyl are administered just before the procedure. Patients are discharged within an average of 3 hours after the procedure, once the sedation effect wears off. Patients were evaluated on the 15th day, 6th month, and 1, 2, 4, and 6 years after the procedure.

Figure 1

Change in VAS Score Over Time



3. Results

Pain scores in the pre-treatment (Pre-op) period (ranging from 7 to 10) decreased significantly in the post-treatment periods (15th day, 6 months, 1 year, 2 years, 4 years). In the analysis conducted with the Wilcoxon test, a significant difference was found between pre-op and all post-treatment periods.

P-values (0.00097, 0.0048) indicate that post-treatment VAS scores have significantly decreased compared to the pre-treatment period. This suggests that conventional radiofrequency (RF) treatment applied to patients with trigeminal neuralgia is effective both in the short and long term.

It is particularly noteworthy that pain levels were almost close to zero within the first year (15th day, 6 months, 1 year). This demonstrates that the treatment is highly successful in the short term. However, the recurrence of pain scores in some patients during the 2nd and 4th years (e.g., a p-value of 0.0048 for the 4th year) suggests that the long-term effect of the treatment is not the same for every patient. This implies that pain management and the treatment process should be tailored to individual patient needs.

In the expanded dataset, no significant differences were found between medical treatment types (carbamazepine, pregabalin, gabapentin). All three treatments provided similar reductions in VAS scores. This indicates that the effectiveness of medical treatments is comparable, and they assist in pain management when combined with RF treatment

4. Discussion

In our study, the minimum age was 41 and the maximum age was 68. Additionally, 27 of the patients were female, and 6 were male. In 90% of patients with primary trigeminal neuralgia, symptoms appear after the age of 40, with the most common age range being 40-70 years. It is more prevalent in women than in men, with a female-to-male ratio of 1.5:1. The patient series we examined in our study was consistent with both the age of onset and the female-to-male ratio of TN. Additionally, all patients met the clinical diagnostic criteria for primary TN.[7] Secondary causes of TN were ruled out in our patients through brain magnetic resonance imaging (MRI) and neurological examination.

In our series,27 patients had mandibular nerve involvement, and 6 had maxillary nerve involvement. The first treatment option for primary TN is medication. The initial approach always consists of medication.[1] Carbamazepine, oxcarbazepine, amitriptyline, gabapentin, and pregabalin are the most commonly used drugs. In

our series, 18 patients were using carbamazepine, 12 were using pregabalin, and 3 was using gabapentin. Medication treatment was discontinued in all patients after the procedure. As shown in figure 1, the VAS score decreased to 0 in 18 patients on the 15th day, to 2 in 12 patients, and to 1 in 3 patients. The VAS score exceeded 5 in 3 patients in the 2nd year and in 15 patients in the 4th year, and conventional RFT was repeated for these patients. Pregabalin 75 mg was started for all patients between the recurrence of pain and the interventional procedure, and it was discontinued once the pain decreased after the procedure. No side effects were observed in the patients.

Due to the higher morbidity-mortality, complication rates, and longer hospitalization period in microvascular decompression surgery, conventional radiofrequency is considered the first choice among percutaneous interventional treatment options.[8] In conventional RF, sufficient cooperation with the patient and the repeatability of the procedure reduce the complication rate and increase the success rate compared to other percutaneous interventional methods. The 25-year follow-up of 1600 patients by Kanpolat and colleagues demonstrated that when applied by an experienced clinician adhering to application rules, complication rates were very low, and procedure success was very high.[9] Therefore, success should be increased throughout the procedure by cooperating both radiographically and with the patient. No complications were observed in our series.

The findings of this study present a significant innovation when compared to previous studies in the literature.[10-14] In particular, the statistically significant decrease in preoperative pain in postoperative evaluations is consistent with the studies in the literature. This result provides a new perspective to the trigeminal neuralgia literature and provides important clues on how the findings can be used in a larger patient population or in clinical practice. However, some limitations should be taken into account in order to objectify the findings of this study and reach broader conclusions. Since the study sample was limited to a single clinic, the results have some limitations in terms of generalizability. In addition, since the methodology used is an observational design, more caution should be exercised in terms of causal relationships. Future studies should confirm these findings with larger and more diversified samples and using different methodological approaches and fill the gaps in the current literature.

5. Conclusion

This study demonstrated the efficacy of conventional radiofrequency thermocoagulation in the treatment of classic trigeminal neuralgia. The high pretreatment pain scores decreased significantly after treatment, and the short-term results were promising. However, long-term pain recurrence was observed in some patients, emphasizing the importance of individual treatment planning. It was concluded that RF thermocoagulation should be considered as the first choice compared to microsurgery, with its low complication rates and short hospital stay. The limited sample size and single-center nature of our study may affect the generalizability of the findings; therefore, future studies with larger and more diverse sample groups will reinforce the validity of these results.

Statement of ethics

Ethical permission was obtained from the Adana City Training and Research Hospital Clinical / Human Research Ethics Committee for this study date on May 26, 2024, and decision number 59 and Helsinki Declaration rules were followed to conduct this study.

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

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

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Relationship Between the Angle of Popliteal Artery Trifurcation Branches and Atherosclerosis Burden in Chronic Peripheral Arterial Disease

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Abstract

Aim: The aim of this study was to investigate the relationship between the angles of the popliteal artery trifurcation branches and atherosclerosis burden in patients with peripheral arterial disease (PAD).

Methods: Digital subtraction angiography (DSA) images of patients who underwent angioplasty for lower extremity PAD between April 2021 and 2023 were retrospectively analyzed. The study excluded non-type 1a popliteal artery branching variations, critical stenosis or occlusion cases, and those with motion artifacts or previous femoropopliteal bypass operations. Angles of the anterior tibial artery (ATA), posterior tibial artery (PTA), and fibular artery (FA) were measured. Atherosclerosis burden was scored from 0 to 18 based on luminal narrowing and occlusion in each artery. Spearman correlation analysis was used to examine the relationship between trifurcation angles and atherosclerosis burden.

Results: A total of 68 patients were included, with a mean age of 65 years. Angioplasty was performed on the right side in 56% of patients and on the left side in 44%. The ATA angle showed a weak positive correlation with atherosclerosis burden (r_s = 0.144, p = 0.29). In contrast, PTA and FA angles exhibited moderate (r_s = 0.398, p = 0.001) and strong (r_s = 0.599, p < 0.001) positive correlations, respectively.

Conclusions: This study highlights the significant association between the angulation of popliteal artery trifurcations and atherosclerosis burden, suggesting that vessel geometry should be considered in the management of PAD.

Keywords: *Atherosclerosis, peripheral arterial disease, angioplasty, trifurcation artery, digital subtraction angiography*

1. Introduction

Peripheral artery disease (PAD) in the lower limbs is an atherosclerotic disease of the arteries supplying the legs.[1] PAD affects more than 230 million adults worldwide and is associated with an increased risk of several adverse clinical outcomes.[2] Risk factors for PAD include smoking, diabetes, high blood pressure, high cholesterol, advanced age, family history of heart disease, obesity, physical inactivity, poor diet, and certain chronic conditions such as kidney disease and metabolic syndrome.[2,3]

The popliteal artery, a major conduit in the lower extremities, often exhibits variations in branching, particularly trifurcation. A classification for the variation of popliteal artery trifurcation branches has been defined.[4] The popliteal artery typically bifurcates into its terminal branches within the posterior compartment of the leg.

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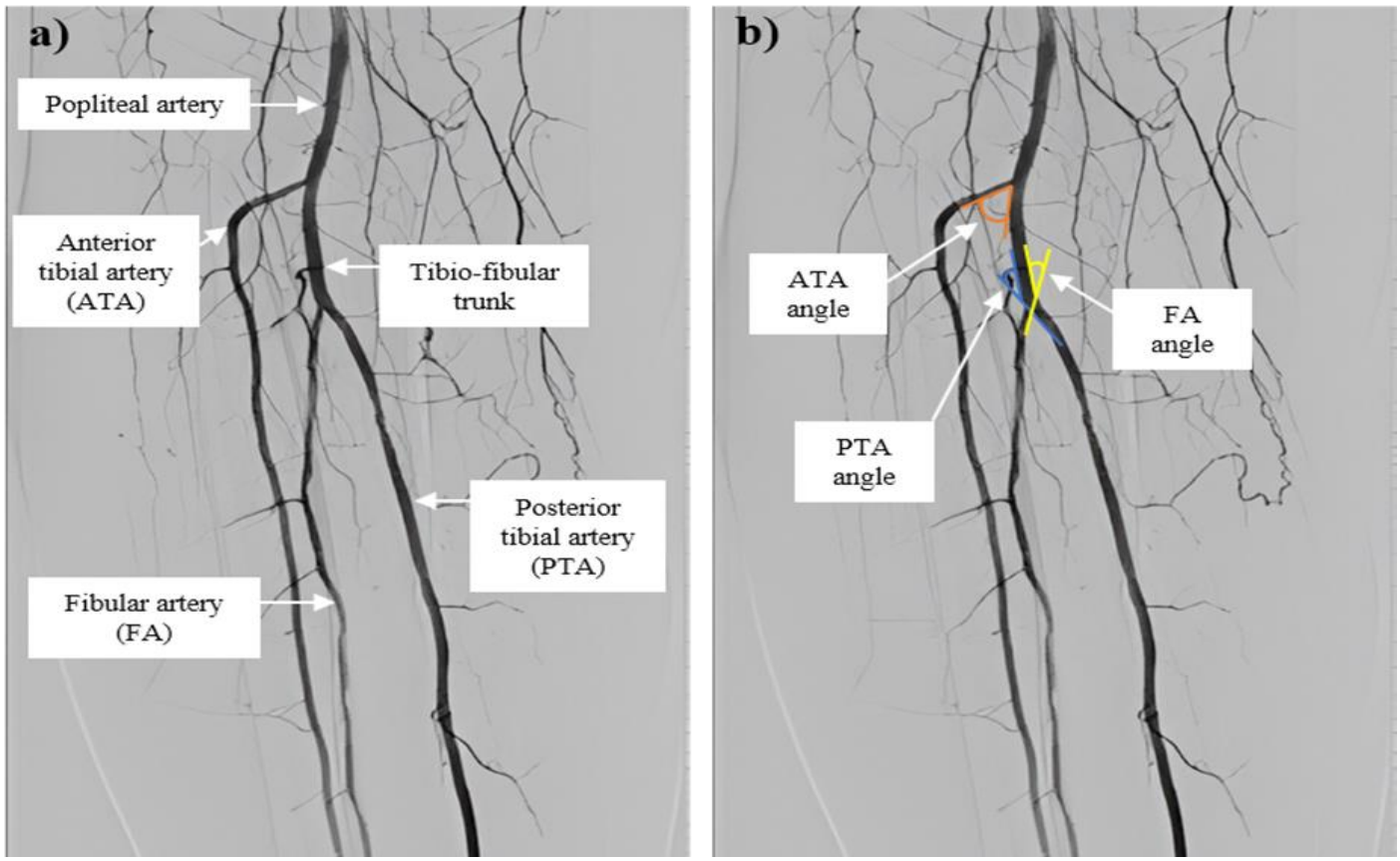
The first branch is the anterior tibial artery (ATA), followed by the tibio-fibular trunk, which further divides into the fibular artery (FA) and the posterior tibial artery (PTA) (**Figure 1**). Many studies have reported that this branching pattern, classified as type 1a, is observed in almost 90% of cases.[5,6] Understanding the variations in popliteal artery trifurcations is essential for surgeons and interventional radiologists when performing procedures such as bypass surgeries or angioplasty in the lower extremities. Although there are many studies in the literature to describe the variations of the popliteal trifurcation branches, we did not find any studies investigating the variations in the degree of angulation of these branches and their possible effects.

The endothelium that lines the vascular system is highly susceptible to hemodynamic forces that exert themselves at the vessel's luminal surface in the direction of blood flow. While numerous biochemical and mechanical factors regulate endothelial cells, wall shear stress (WSS) is one of the most critical regulators of endothelial functions.[7] Studies have highlighted the importance of vessel shape, velocity distribution, and WSS in atheroma location, progression, and clinical outcomes.[8-11] One study reported that an increase in the angle of branching of the coronary arteries creates more

Figure 1
A 58-year-old woman with a right diabetic foot wound



a) The DSA image shows a type 1a trifurcation branching pattern in the popliteal artery.
b) An angle measurement of the popliteal artery trifurcation branches is shown. The angle of the anterior tibial artery (ATA) is orange; the angle of the posterior tibial artery (PTA) is blue; and the angle of the fibular artery (FA) is yellow.

turbulent and oscillatory flow, and that this flow contributes to endothelial dysfunction, which is the precursor to atherosclerosis, by reducing WSS.[12] In light of these data, the aim of this study was to investigate whether there is an association between the degree of angulation in the trifurcation branches of the popliteal artery and the burden of atherosclerosis.

2. Materials and methods

The local ethics committee approved this study (ethics no. 565473, date: 12.07.2024). Informed consent was not obtained from patients due to the retrospective nature of the study.

2.1. Study population

Digital subtraction angiography (DSA) images of 104 patients undergoing percutaneous transluminal angioplasty (PTA) for lower-extremity peripheral artery disease at our Interventional Radiology Unit between April 2021 and 2023 were retrospectively evaluated. Other branching variations of the popliteal artery other than type 1a were excluded from the study, as were cases of critical stenosis and/or occlusion of the superficial femoral and popliteal arteries, along with those exhibiting motion artefacts, the presence of metallic orthopaedic materials, a history of femoropopliteal bypass operations, and below-knee amputations. For the remaining 68 patients, data were collected on age and sex, smoking, hypertension, high cholesterol, renal dysfunction, heart failure, and diabetes.

2.2. Digital subtraction angiography

After skin sterilization and local anaesthesia, a 6F introducer was inserted into the superficial femoral artery using the Seldinger method under ultrasound guidance. Diagnostic images were then obtained with four separate DSA scans using non-ionic contrast material. For each scan, a 10-cc bolus of contrast was administered. The first DSA image was obtained for the superficial femoral artery, the second for the femoropopliteal artery, the third for the trifurcation arteries, and the last for the pedal arteries.

2.3. Image analysis

In the DSA image, including the femoropopliteal region, angle measurements were performed separately for ATA, PTA, and FA. The ATA angle was measured from the branching site of the popliteal artery, and the PTA and FA angles were measured from the branching site of the tibio-fibular trunk. The method used for measuring the angle is shown in Figure 1.

A scoring system was designed to quantify the atherosclerosis burden of the trifurcation arteries. The segment of the trifurcation arteries from the origin to the intermalleolar level was divided into three equal parts: proximal, middle, and distal (Figure 2). Each equal segment was scored between 0 and 6, according to the visual scoring system below.

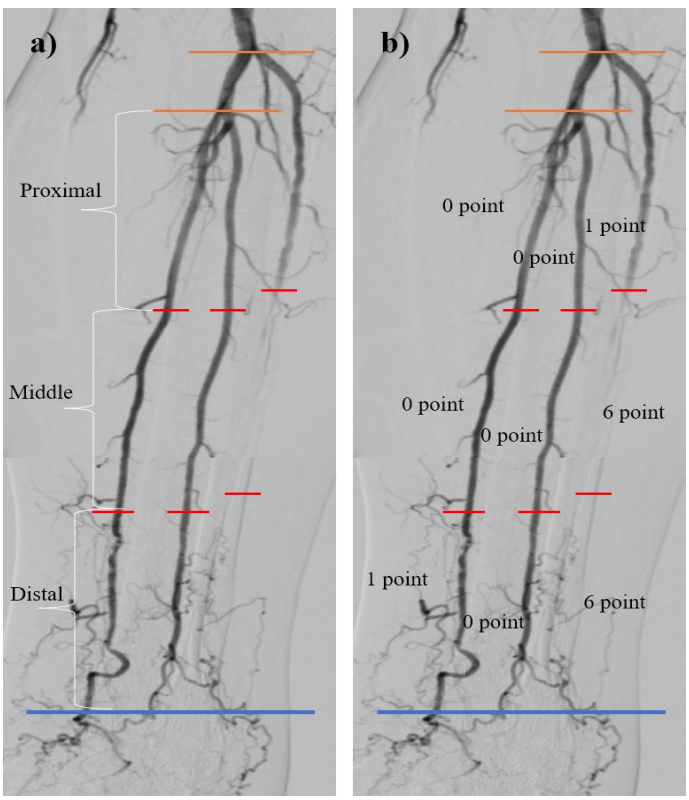
0 points: *completely normal lumen.*
1 point: *<50% luminal narrowing affecting less than half of the segment.*

2 points: *<50% luminal narrowing affecting more than half of the segment.*
3 points: *≥50% luminal narrowing affecting less than half of the segment.*
4 points: *≥50% luminal narrowing affecting more than half of the segment*
5 points: *total occlusion affecting less than half of the segment*
6 points: *total occlusion affecting more than half of the segment*

In total, an atherosclerosis burden score between 0 and 18 was calculated for each trifurcation artery. An example of the scoring system is shown in Figure 2. To enhance the accuracy of the subjective scoring system used for assessing atherosclerosis burden, measurements were performed by two independent observers.

Figure 2

A 72-year-old male patient with an ischaemic wound on the left foot.



a) The division of each trifurcation artery into proximal, middle, and distal segments is shown. Orange lines show the origin of ATA, PTA, and FA; blue lines show the intermalleolar line; and red lines show the division of the arteries into three equal segments.
b) To calculate the atherosclerotic burden of the trifurcation arteries, the scores given to each segment are shown. In total, ATA received 13 points, PTA 1 point, and FA 0 points.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0, SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used to determine whether the data set conformed to a normal distribution. Normally distributed data were expressed as mean ±standard deviation, and non-normally distributed data were expressed as median (25th–75th percentile).

The level of agreement between the observers was evaluated using the intraclass correlation coefficient (ICC). An ICC value above 0.75 was considered to indicate high agreement, a value between 0.4 and 0.75 was considered to indicate moderate agreement, and a value below 0.4 was considered to indicate low agreement.

The relationship between the angle of the trifurcation arteries and the burden of atherosclerosis was examined using the Spearman correlation test. In a positive or negative direction, a Spearman correlation coefficient (r_s) of 1 indicates an excellent monotonic relationship; less than 0.4 to 0.7 indicates a moderate relationship; less than 0.2 to 0.4 indicates a weak relationship; and 0 indicates no monotonic relationship. $p < 0.05$ was considered statistically significant.

3. Results

A total of 68 patients were included in the study. The mean age was 65 ± 11 years. Of the patients, 56 (82%) were male and 12 (18%) were female. Smoking was reported in 47 patients (69%). Hypertension was prevalent in 59 patients (87%), while 10 patients (15%) had high cholesterol levels. Renal dysfunction was observed in 34 patients (50%) and heart failure in 29 patients (43%). Additionally, 55 patients (81%) were diagnosed with diabetes mellitus (Table 1).

Table 1

Demographic and clinical features of the patients

n: 68	n(%)
Age	65±11
Gender (male-female)	56 (82%) - 12 (18%)
Smoking	47 (69%)
Hypertension	59 (87%)
High cholesterol	10 (15%)
Renal dysfunction	34 (50%)
Heart failure	29 (43%)
Diabetes mellitus	55 (81%)

Angioplasty was performed on the right side in 38 patients (56%), and on the left side in 30 patients (44%). The trifurcation angles were 58° ± 11° for ATA, 23° ± 8° for PTA, and 15° ± 8° for FA.

Table 2

Presence and burden of atherosclerotic lesions in the trifurcation arteries

n: 68	
Angioplasty (right-left)	38 (56%) - 30 (44%)
Trifurcation arteries angle degree	
• Anterior tibial artery	58°±11°
• Posterior tibial artery	23°±8°
• Fibular artery	15±8°
Localizations of atherosclerotic lesions	
• Anterior tibial artery	56 (82%)
• Posterior tibial artery	50 (73%)
• Fibular artery	27 (40%)
Burden of atherosclerosis	
• Anterior tibial artery	11 (5-15) points
• Posterior tibial artery	9 (3-16) points
• Fibular artery	3 (0-11) points

Atherosclerotic lesions were located on ATA in 56 patients (82%), on PTA in 50 patients (73%), and on FA in 27 patients (40%). Atherosclerosis burden was calculated as 11 (5–15) points for the ATA, 9 (3–16) points for the PTA, and 3 (0–11) points for the FA (Table 2). An ICC value of 0.82, indicating high agreement, was obtained.

The results of Spearman's correlation test between the trifurcation angle and the burden of atherosclerosis showed the following monotonic relationships: For the ATA, Spearman's rho (r_s) was 0.144 with a p-value of 0.29, suggesting a weak positive monotonic relationship that is not statistically significant. For the PTA, Spearman's rho was 0.398 with a p-value of 0.001, indicating a moderate positive monotonic relationship that is statistically significant. For the FA, Spearman's rho was 0.599 with a p-value of less than 0.001, indicating a strong positive monotonic relationship that is statistically significant (Table 3).

Table 3

Spearman's correlation test results between trifurcation angle and atherosclerosis burden

	rs	p
Anterior tibial artery	0,144*	0,29
Posterior tibial artery	0,398*	0,001
Fibular artery	0,599*	<0,001

rs (Spearman's rho), Spearman correlation coefficient.
**Correlation is significant at the 0.01 level (2-tailed).*

4. Discussion

The results of this study showed varying degrees of correlation between the angles of different trifurcation branches and the extent of atherosclerosis, highlighting the potential impact of vessel geometry on the progression of atherosclerotic disease.

The results showed that the ATA angle had a weak positive correlation with atherosclerotic burden, which was not statistically significant. Conversely, the angles of the PTA and FA showed moderate and strong positive correlations with atherosclerosis burden, respectively, both of which were statistically significant. This finding indicates that larger angles of the PTA and FA are associated with a greater severity of atherosclerosis in these branches. These correlations suggest that larger branch angles may contribute to disturbed flow patterns, such as increased turbulence and oscillatory shear stress, which are known to promote endothelial dysfunction and atherogenesis.[13] Previous research has shown that regions of low and oscillatory wall shear stress are more prone to atherosclerosis due to the resulting endothelial injury and inflammatory responses.[14] Our study confirms these findings in the context of the popliteal artery trifurcation and highlights the importance of considering vessel geometry in the assessment and management of PAD. Since we could not find a similar study in the literature, we could not compare our results, but there are studies reporting that vessel geometry is associated with atherosclerosis formation in coronary arteries.[8,15,16]

The clinical implications of this study are important for interventional radiologists and vascular surgeons. Understanding the relationship between trifurcation angles and atherosclerotic burden can inform the planning and execution of endovascular procedures. For example, when performing angioplasty or stenting, identifying regions of increased atherosclerotic burden associated with specific vessel angles may help to anticipate complications and optimise treatment strategies.

This study had several limitations. Firstly, the visual scoring used to calculate the burden of atherosclerosis is an estimate. The development and use of more objective measurement methods, such as automated software-based analysis, should be considered in future studies to further reduce potential biases. In addition, it is clear that atherosclerosis is not only associated with variations in vessel geometry. There are many possible etiological factors. However, this study was designed to investigate the effect of a single possible factor. Finally, the exclusion of variations other than type 1a aimed to evaluate the effect of vessel geometry on atherosclerotic burden in a more homogeneous group of patients. However, this limitation may limit the generalizability of the findings to a larger population of patients with different popliteal artery variations.

5. Conclusion

In conclusion, this study found a significant association between the degree of angulation of the popliteal artery trifurcations and atherosclerotic burden. Investigating the effects of interventions designed to alter flow patterns and shear stress in patients with unfavourable trifurcation angles may provide new therapeutic avenues to reduce PAD burden. Future research should aim to confirm these findings in larger prospective cohorts and explore the underlying mechanistic pathways linking vascular geometry and atherosclerosis.

Statement of ethics

Ethical permission was obtained from the Aydın Adnan Menderes Faculty of medicine Clinical / Human Research Ethics Committee ethics no. 565473, date: 12.07.2024

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by AT&AA. The first draft of the manuscript was written by AT&AA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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The Effect of Discharge Education and Post-Discharge Telephone Counseling on Quality of Life in Patients Undergoing Radical Prostatectomy: A Randomized Controlled Study

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Abstract

Aim: This study aims to determine the effect of model-based discharge education, and post-discharge telephone counseling on patients who have undergone radical prostatectomy on their quality of life.

Methods: This randomized controlled study consisted of patients who underwent radical prostatectomy surgery and completed with a total of 42 patients, 20 of whom were in the experimental and 22 in the control group. The experimental group patients and their relatives were given model-based discharge education and patients were called every two weeks after the operation. The control group received standard care. The patients' quality of life was evaluated the day before the operation, and at the 6th and 12th weeks after surgery. The data were collected with the "Personal Information Form", and "Short Form-12 Health Survey (SF-12)".

Results: 55.0% of the patients in the experimental group and 54.5% of the patients in the control group experienced urinary incontinence; 45.0% of the experimental group patients and 50.0% of the control group patients experienced erectile dysfunction at the 12th postoperative week. The experimental group had statistically significantly higher SF-12 mental component scores in the 12th week than the control group ($p < 0.05$).

Conclusions: Model-based discharge education and post-discharge telephone counseling for patients who had radical prostatectomy surgery were effective in the mental dimension of the patient's quality of life, but not in the physical dimension. Providing patients with different information channels will support the psychological dimension of their quality of life.

Keywords: *Counseling, education, quality of life, nursing, prostatectomy.*

1. Introduction

Prostate cancer (PCa) is the most common type of cancer in men and ranks second among the causes of cancer deaths in men worldwide.[1-3] The lifetime risk of PCa is 15%, and the mortality rate is 2.9%[4]. PCa has become a significant health problem today, especially in developed countries with an aging population.[1,2]

Various treatment methods are used in the treatment of PCa, depending on factors such as the stage of cancer, the overall health status of patients, life expectancy, and patient preferences.[2]

One of the treatment methods for PCa is radical prostatectomy (RP). RP is a highly effective and gold-standard surgical method for the treatment of particularly early-stage and localized PCa patients with a life expectancy of over 10 years.[2-4] RP is a procedure in which the prostate gland, lymph nodes, and seminal vesicles are removed.[2] After RP, patients have to deal with many complications that negatively affect their quality of life.[5] These complications can have many negative effects on patients' lives, causing psychosocial changes such as anxiety, depression, difficulty in social interaction, and low self-esteem.[6-8] The most important problems of the patients in the first 4 months after discharge are catheter care, pain control, urinary incontinence, and erectile dysfunction following catheter withdrawal[6]. Especially during the first three months after surgery, patients who undergo RP face a significant period in which they deal with problems related to the surgery and try to cope with them.[9] Patients need the support of health personnel to explain their surgical problems and to get help.[6] Patients with RP require cognitive,

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psychological, and functional support.[6,10] In this challenging process, nurses who have important roles and responsibilities aim to accelerate the recovery process and improve the quality of life of patients through their comprehensive care.[9]

Nursing interventions after prostate surgery focus on pain management, urinary catheter care, nutrition, exercise, pelvic muscle exercises, patient education, and psychosocial counseling.[10] Various methods are available to provide support, including informative brochures, preoperative counseling, telephone support, educational videos, and various educational programs. PCa patients undergoing surgical intervention need accurate information before, during, and after treatment.[11] However, a systematic review has shown that patients undergoing prostatectomy do not receive adequate training and support[12]. Patient education and consultancy are important in meeting patients' information needs for their self-care skills, and sense of control and helping patients manage the negative effects associated with RP thus helping to support their physical and psychological well-being.[8,10,12]

Today, the approach of early discharge of patients to their homes limits the adequate patient education about the home care needs of the patient. As a result, the patients leave the hospital with a lack of information about the management of complications and home care needs. Therefore, discharge training is very important[6]. Discharge education is important for coping with complications and the improvement of a patient's quality of life. Nurses play a key role in discharge planning. Discharge education is a process of preparing the patient, their family, and their close circle for the care information and responsibilities they may need after discharge.[13] Educational interventions increase the patient's knowledge and competency on how to deal with pain, incisions, drains, and the catheter.[14] In the postoperative period, anxiety, fatigue, and pain due to surgery can reduce the effectiveness of training. For this reason, in addition to verbal education, patients can be supported and the effectiveness of discharge education can be increased by giving a written education brochure or booklet and visiting the patients at home or following them by telephone in the early postoperative period.[6]

The quality of nursing care received by patients during the treatment process will depend on the complete and accurate implementation of all steps of the nursing process, as well as the application of a model or theory that supports the scientific nature of the care[15]. Roper-Logan-Tierney Model of Nursing Based on Activities of Living is one of the models frequently used in nursing. This model, which is compatible with Maslow's hierarchy of basic human needs, identifies 12 activities that patients and healthy individuals perform to maintain their daily lives.[15,16] The model includes all the relationships between the elements that make up an individual's life and is used to protect and improve the health of individuals. It consists of five main components: “lifespan”, “12 activities of living”, “factors affecting life activities”, “dependent-independence continuum” and “individuality in living”. The model aims to prevent or solve problems related to daily living activities affected by the disease rather than treating the disease.[17] This model evaluates the individual as a whole, determines all the needs of the individual, and guides the implementation of the nursing process. Nursing care given to a patient diagnosed with prostate cancer in line with the Nursing Model with classification systems provides diagnosis and planning in a versatile and systematic way. It facilitates clinical decision-making and evaluation of nursing care.[18] Using this model, the holistic nurse identifies the individual's care needs[15,16]. Education and counseling, planned based on a model appropriate for patient needs, can improve the quality of life of patients and families.[19] It is thought that increasing the communication between patients and health personnel, informing and supporting patients about their post-discharge life will positively affect the quality of life of patients.[6]

1.1. Aim

This study aims to determine the effect of model-based discharge education, and post-discharge telephone counseling on patients who have undergone radical prostatectomy on their quality of life.

1.2. Study Hypotheses

Hypothesis 1. The experimental group who receives discharge education, and post-discharge telephone counseling will have a higher Short Form-12 Health Survey (SF-12) physical component score after education and counseling than that of the control group.

Hypothesis 2. The experimental group who receives discharge education, and post-discharge telephone counseling will have a higher Short Form-12 Health Survey (SF-12) mental component score after education and counseling than that of the control group.

2. Materials and methods

2.1. Design

This was a randomized controlled study.

2.2. Setting

The study was carried out in the urology clinic of a university hospital in Adana, Turkey.

2.3. Sample

The population of the study consisted of patients who underwent radical prostatectomy surgery between June 2022 and January 2023. The inclusion criteria were: (1) being 18 years or older, (2) being literate, (3) able to understand and speak Turkish, (4) not having a hearing impairment, and (5) agreeing to participate in the research. The exclusion criteria were: (1) development of any complications during the surgical intervention, (2) having any psychiatric disorder that will reduce the ability to comprehend and understand, (3) having other types of cancer accompanying PCa, (4) having metastases, and (5) being not agreed to participate in the study.

The sample number of the study was calculated using the G*Power 3.0.10 program after collecting the data from 10 prostatectomy surgery patients (n_1:5; n_2:5). The patients participating in the preliminary study were not included in the study. The results of the power analysis indicated that a minimum sample size of 42 in total was sufficient (n_1:21; n_2:21) with a one-tailed hypothesis, 80% power, 5% margin of error, and an effect size of 0.80 for t-tests[20,21]. Considering the 10% of possible participants lost to follow-up, a total sample of 46 subjects, 23 in each group, was considered. Patients were divided into experimental and control groups using simple randomization methods with a computer-generated randomization table.

2.4. Outcomes

The primary outcome was the quality of life score. The data were collected using the “Personal Information Form”, and the “Short Form-12 Health Survey (SF-12)”.

The Personal Information Form consists of two parts. The first part included information such as the patient’s age, weight, height, marital status, level of education, working status, presence of chronic diseases, clinical stage, American Society of Anesthesiology (ASA) score, and surgical method used. In the second part, urinary incontinence, and erectile dysfunction were questioned. At the 12th postoperative week, patients were asked about the presence of urinary incontinence and erectile dysfunction problems and were evaluated as “yes” or “no”.

Short Form-12 Health Survey (SF-12) was used to assess quality of life. It consists of 12 items in 8 subdimensions. The items on role-physical and role-emotional are dichotomous, to be answered as “yes or no”, while the other items are Likert-type with response options ranging from 3 to 6. The total physical component score (PCS-12) score is obtained from the subdimensions of “general health”, “physical functioning”, “role-physical”, and “bodily pain”; and the to-

tal mental component score (MCS-12) score is obtained from the subdimensions of "social functioning", "role-emotional", "mental health" and "energy". Higher scores indicate better health status. The scale scores range from 0 to 100[22].

2.5. Study Procedures

Patients who volunteered to participate in the study were divided into two groups: experimental and control. Patients in both groups were asked to fill out the first section of the "Personal Information Form" and the "SF-12" one day before the surgery. The experimental group received face-to-face model-based discharge education using an educational booklet, and post-discharge telephone counseling. The patients in the experimental group were called by the counseling researcher every two weeks after the operation and counseling was provided according to their needs. The control group was not given model-based discharge education and post-discharge counseling. No intervention other than standard care was applied to the patients in the control group. Routine/standard care in the clinic includes verbal discharge education without using any materials. Both groups of patients were contacted by phone at the 6th and 12th weeks postoperatively, and they were asked to complete the online Short Form-12 Health Survey. During the call in the 12th week, the presence of urinary incontinence and erectile dysfunction were also inquired and evaluated based on the patient's self-reports as "yes/no" and recorded in the second part of the Personal Information form.

Discharge education: The experimental group patients and their relatives were given model-based discharge education in the patients' room face-to-face one day before the discharge. Although it differed according to the learning status of the patients, the education lasted an average of 30-40 minutes. The patient education booklet was prepared based on the 12 daily living activities specified in the Roper-Logan-Tierney Model of Nursing by the researchers and finalized in line with experts' (2 urology physicians, 2 clinical nurses, and 3 academic nurses) opinions. The education booklet included information about the points patients should pay attention to during the post-operative and post-discharge periods. After the education, the education booklets containing the researcher's telephone number were given to the patients. The patients were informed that the phone number in the booklets belonged to the researcher and that they could contact the researcher whenever they needed.

Post-discharge telephone counseling: Post-discharge counseling was provided by telephone. The patients' needs were determined during the calls by referring to each title in the education booklet. Therefore, the duration of the calls varied depending on the needs of the patients.

2.6. Data collection

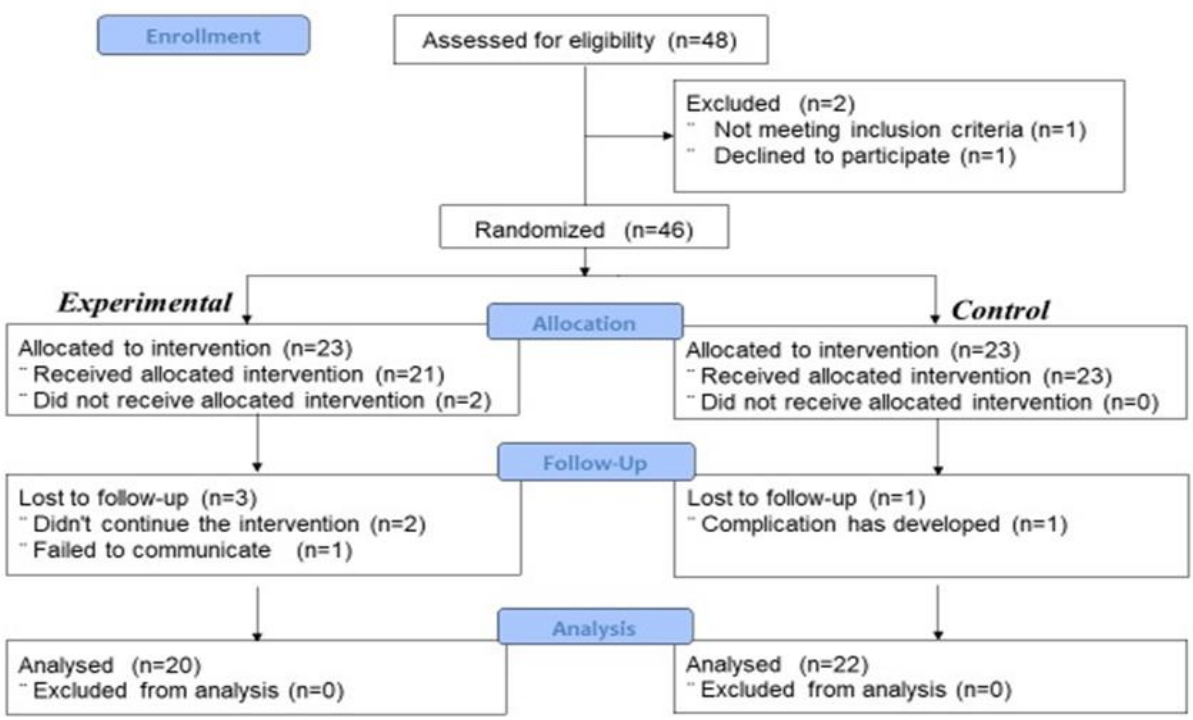
Data were collected at three time points: one day before the operation, 6th and 12th weeks after the operation. The researcher, who provided the education, collected pre-discharge data through face-to-face interviews and post-discharge data using an online survey. The researcher interviewed all patients face-to-face, obtained written and verbal consent, and filled out the "Personal Information Form" and "SF-12" one day before the operation. After discharge, outcome measures were collected in the 6th and 12th weeks after the operation on the online platform.

2.7. Blinding

The statistical analysis was conducted by a researcher who was blinded to the group assignments.

Figure 1

CONSORT 2010 Flow Diagram



2.8. Data analysis

Data analyses were made using IBM SPSS Statistics 24. Skewness and kurtosis values were used to determine the normal distribution. Data were normally distributed, and parametric tests were used[23]. The descriptive statistics, independent samples t-test, repeated measures ANOVA test, and $\chi 2$ cross-tabulation were used.

2.9. Ethical considerations

The study was conducted in conformity with the Helsinki Declaration principles. Approval from the ethics committee was obtained from the Non-Interventional Clinical Research Ethics Committee of the university where the study was conducted (Date: April 8, 2022, Number of meetings: 121, Decision no: 29). Institutional permission was obtained. All patients were informed about the aim of the study, that their participation was voluntary, and that their participation or withdrawal from the study would not affect their treatment and care.

3. Results

Figure 1 is the trial CONSORT 2010 diagram showing participant flow through the study.[24] The study was completed with a total of 42 patients, 20 of whom were in the experimental and 22 in the control group.

3.1. Homogeneity test

The experimental and control groups found no significant differences in descriptive characteristics ($p > 0.05$, Table 1). No statistically significant difference was found between the experimental and control groups before the surgery in SF-12 scores ($p > 0.05$, Table 2).

3.2. Hypothesis tests

No statistically significant difference was found between the experimental and control groups in the 6th, and 12th weeks after the surgery in SF-12 physical component scores ($p > .05$, Table 2). Thus, Hypothesis 1 was not supported.

There was a statistically significant difference between the groups in the postoperative 12th week of SF-12 mental component scores ($t= 2.381$, $p< 0.05$). The experimental group (40.86 ± 7.00) had statistically significantly higher SF-12 mental component scores in the 12th week compared to the control group (36.41 ± 5.03). Thus, Hypothesis 2 was supported (Table 3).

There was no statistically significant difference in the SF-12 physical and mental component scores between experimental groups at different stages preoperatively and postoperatively ($p > .05$). However, there was a statistically significant difference in the SF-12 mental component scores between control groups in different stages ($F=7.185$, $p < .05$). It was determined that the preoperative SF-12 mental component scores (44.93 ± 9.32) differed statistically significantly from the 6th-week postoperative scores (42.26 ± 9.49) of the control group. Also, there was a statistically significant difference between the 6th-week (42.26 ± 9.49) and 12th-week scores (36.41 ± 5.03) of SF-12 mental component scores of the control group (Table 3).

55.0% of the patients in the experimental group and 54.5% of the patients in the control group experienced urinary incontinence; 45.0% of the experimental group patients and 50.0% of the control group patients experienced erectile dysfunction at the 12th postoperative week. There were no statistically significant differences between the groups regarding urinary incontinence and erectile dysfunction at the 12th postoperative week ($p > 0.05$, Table 4).

Table 1

Comparison of descriptive characteristics of the patients (n=42)

	Experimental Group (n=20)		Control Group (n=22)		Test
	$\bar{X} \pm SD$	Median [Min-Max]	$\bar{X} \pm SD$	Median [Min-Max]	
Age	65.20 ± 6.42	65.5 [48-73]	63.50 ± 5.06	63.0 [55-73]	$t= .957^a$ $p= .844$
Body Mass Index (kg/m²)	25.77 ± 3.31	24.7 [21.7-33.9]	25.93 ± 1.96	26.1 [22.9-29.7]	$Z= -1.057^b$ $p= .290$
	n	%	n	%	
Education level					
• **Primary school**	6	30.0	5	22.7	$\chi^2= .330^c$ $p= .848$
• **High school**	12	60.0	15	68.2	
• **University**	2	10.0	2	9.1	
Working status					
• **Yes**	8	40.0	14	63.6	$\chi^2= 2.346^c$ $p= .126$
• **No**	12	60.0	8	36.4	
Marital status					
• **Married**	17	85.0	21	95.5	$\chi^2= 1.329^c$ $p= .249$
• **Single**	3	15.0	1	4.5	
Chronic disease					
• **Yes**	9	45.0	9	40.9	$\chi^2= .072^c$ $p= .789$
• **No**	11	55.0	13	59.1	
Clinical Stage					
• **1**	10	50.0	15	68.2	$\chi^2= 1.437^c$ $p= .231$
• **2**	10	50.0	7	31.8	
Surgery method					
Laparoscopic	17	85.0	20	90.9	$\chi^2= .394^c$ $p= .555$
Open Surgery	3	15.0	2	9.1	
ASA					
• **1**	7	35.0	7	31.8	$\chi^2= .048^c$ $p= .827$
• **2**	13	65.0	15	68.2	

[a] *Independent Sample-t;* [b] *Mann-Whitney U;* [c] *Pearson-χ^2*

Table 2

Comparison of SF-12 physical component of patients during different stages

SF-12 Physical	Experimental Group (n=20)		Control Group (n=22)		Test
	$\bar{X} \pm SD$	Median [Min-Max]	$\bar{X} \pm SD$	Median [Min-Max]	
Preoperative	40.96 ± 4.06	41.6 [34.1-47.2]	39.14 ± 6.70	40.4 [27.1-46.1]	*t*=1.073[a] *p*= .291
6th week	38.77 ± 4.27	38.7 [32.1-50.9]	37.38 ± 5.71	37.8 [25.6-47.5]	*t*= .903[a] *p*= .372
12th week	38.95 ± 4.45	37.9 [30.5-46.1]	36.76 ± 5.49	37.7 [27.1-45.0]	*t*=1.407[a] *p*= .167
Test	F=2.240[b] *p*= .135		F=2.166[b] *p*=.141		

[a] *Independent Sample-t*, [b] *Repeated Measures ANOVA*

Table 3

Comparison of SF-12 mental component of patients during different stages

SF-12 Mental	Experimental Group (n=20)		Control Group (n=22)		Test
	$\bar{X} \pm SD$	Median [Min-Max]	$\bar{X} \pm SD$	Median [Min-Max]	
Preoperative (0)	43.7 ± 6.86	44.0 [26.5-53.7]	44.93 ± 9.32	47.0 [25.2-57.5]	*t*= -.445[a] *p*= .659
6th week(1)	41.98 ± 6.75	43.0 [26.4-53.8]	42.26 ± 9.49	42.5 [24.1-57.4]	*t*= -.108[a] *p*= .914
12th week(2)	40.86 ± 7.00	40.3 [27.3-51.7]	36.41 ± 5.03	37.1 [20.2-44.7]	*t*= 2.381[a] *p*= .022
Test	F= 2.580[b] *p*= .103		F= 7.185[b] *p*= .004 [0-2] [1-2]		

[a] *Independent Sample-t* [b] *Repeated Measures ANOVA*

Table 4

The status of urinary incontinence and erectile dysfunction at the 12th week after surgery (n=42)

	Experimental Group (n=20)		Control Group (n=22)		Test
	n	%	n	%	
Urinary Incontinence					
• **Yes**	11	55.0	12	54.5	χ^2= .001[a]
• **No**	9	45.0	10	45.5	*p*= .976
Erectile Dysfunction					
• **Yes**	9	45.0	11	50.0	χ^2= .105[a]
• **No**	11	55.0	11	50.0	*p*= .746

[a] *Pearson-χ^2*

4. Discussion

The discharge education and post-discharge counseling provided to different patient groups have been shown to have a positive impact on patient outcomes and can be effective in improving their quality of life[25,26]. While there was no significant difference in SF-12 physical component scores between the experimental and control groups at the 6th and 12th weeks after surgery, SF-12 mental scores were significantly higher in the experimental group than in the control group at the 12th week. In this regard, it was concluded that model-based discharge education and post-discharge telephone counseling for patients who had radical prostatectomy surgery were effective in the mental dimension of the patient's quality of life, but not in the physical dimension.

In a study, it was generally found that RP did not have a long-term negative effect on the functional scales of the quality of life questionnaire over one year, but a temporary decrease in role functioning was observed at three months, which returned to baseline at 12 months[27]. In a qualitative study investigating men's post-radical prostatectomy experiences, telephone and face-to-face interviews were conducted with patients after discharge. Comprehensive written and verbal information before the surgery was not sufficient to manage the postoperative symptoms. Telephone follow-up helped promote adjustment after surgery and reduced anxiety caused by the side effects of surgery and unanswered questions[28]. In our study, the mental dimension of the quality of life of patients in the experimental group was higher than the control group at 12 weeks after surgery, while there was no significant difference be-

tween the groups in terms of the physical dimension. In this study, the absence of differences in the physical dimension of quality of life between groups in the postoperative period can be associated with the presence of physical problems, especially erectile dysfunction and urinary incontinence, after RP. Additionally, there were no differences between the groups in terms of these symptoms, and they were evenly distributed. This situation suggests the need for longer-term interventions and evaluations to alleviate the symptoms. However, the significant difference between the groups in the mental dimension can be considered as an indication that the discharge education and counseling given to patients based on the Nursing Model had an impact on changing the mental dimension of their quality of life. In the literature, it is also recommended that patients who have undergone RP use educational resources such as websites, videos, and written materials for coping with complications and be given a phone number/email address that they can access when they need to express their concerns, which makes them feel more secure. In addition, the importance of patients feeling that they can reach healthcare professionals is emphasized in the literature[7]. Studies have reported that adequate support and education given to patients who have undergone RP contribute to shorter recovery times and increased self-efficacy and self-care skills[8,29,30]. A study has found that guiding patients with preoperative education and counseling tailored to their needs is effective in improving patient-reported sexual function outcomes and optimizing patient satisfaction after surgery[9]. In a randomized controlled study conducted with patients who underwent laparoscopic radical prostatectomy, patients were divided into conventional nursing and psychoeducational intervention groups. In the study, it was determined that 3 months after catheter removal, patients in the psychological nursing intervention group had lower symptoms of anxiety and depression and higher quality of life[31]. It can be said that education tailored to the needs of patients undergoing prostatectomy and based on a model has positive effects on their quality of life.

In this study, it was determined that there was a significant decrease in the mental dimension of the quality of life of patients in the control group after surgery. The decrease in the quality of life of patients after surgery suggests that it may be related to various complications associated with RP. In a study examining changes in quality of life after treatment in patients with localized and metastatic PCa, it was found that there was a deterioration in the quality of life in every time interval measured, and the parameter most affected in the RP group was social function[32]. However, in this study, while the deterioration in the quality of life of patients in the mental dimensions of the control group was significant, the lack of significance in the decrease in the experimental group may be related to the use and perception of the provided education and educational booklets as a source of information for patients to access. This study will make it possible to understand patient needs better and will help improve the quality of care to better respond to these needs.

4.1. Limitations

This study has some limitations. The fact that the effects of the training provided were not evaluated after the 12th week after surgery can be considered a limitation. The limited number of samples may affect the generalization of the results. Another limitation of our study is that chronic illnesses of the patients were considered in a general manner as either present or absent. However, each chronic disease may contribute to the patient's comorbidity index to varying extents.

5. Conclusion

It has been determined that discharge education and counseling provided to patients with RP surgery, based on a model, was effective on the mental dimension of patients' quality of life, but not on the physical dimension. The use of new technologies and information channels can enhance the effectiveness of educational interventions in PCa patients. This study provides support for further investigation of the impact of model-based discharge education and counseling on improving the quality of life in men with PCa.

Statement of ethics

This study was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Approval date: April 8, 2022; Number:121/29).

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

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

Author Contributions

Research idea: İ.K.T., S.D.D., Ş.Y., S.A., Design of the study: İ.K.T., S.D.D., Ş.Y., S.A., Acquisition of data for the study: İ.K.T., Ş.Y., Analysis of data for the study: S.D.D., Interpretation of data for the study: S.D.D., Drafting the manuscript: İ.K.T., S.D.D., Ş.Y, Revising it critically for important intellectual content: İ.K.T., S.D.D., Ş.Y., S.A. Final approval of the version to be published: İ.K.T., S.D.D., Ş.Y., S.A.

Supplementals

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A retrospective study of anesthesia management in patients operated for neuromuscular scoliosis

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Abstract

Aim: Scoliosis frequently develops as a complication of neuromuscular diseases, often progressing and necessitating surgical intervention. Although complications can arise in spinal fusion surgery for all types of scoliosis, they are more frequent during and after the procedure in cases of neuromuscular scoliosis.

Methods: After receiving approval from the ethics committee of our hospital, this study conducted a retrospective review of patient files from individuals who underwent surgery for neuromuscular scoliosis at Ankara Training and Research Hospital between 2008 and 2012. A total of 26 patient files were analyzed. Patient parameters including age (years), gender (female (F), male (M)), weight (kg), presence of neuromuscular disease, concomitant cardiovascular and respiratory conditions, as well as other systemic anomalies and diseases, spirometry findings (FEV1, FVC, FEV1/FVC), nutritional status (total protein, albumin), pre-operative hemoglobin (Hg) and hematocrit (Htc) levels, Cobb angle index, angle direction, type of surgical approach (anterior or posterior), muscle relaxants utilized, additional dosage requirements, operation duration, intraoperative bleeding volume (ml), transfusion volume (ml), and intraoperative complications were documented.

Results: As the Cobb angle increased, several factors were affected: the duration of the operation was extended ($p < 0.05$), there was an increase in blood loss ($p = 0.012$), and more blood transfusions were required ($p = 0.32$). Furthermore, there was a correlation between increasing age and the amount of blood transfused ($p = 0.035$).

Conclusions: It has been concluded that a comprehensive preoperative assessment is crucial, as it can offer valuable insights into anesthesia management both before and after surgery for scoliosis. Therefore, conducting a detailed preoperative evaluation is essential for patients undergoing these procedures

Keywords: *Scoliosis, anesthesia, spinal fusion*

1. Introduction

Scoliosis is characterized by a sideways curvature of the spine exceeding 10 degrees, as determined by the Cobb method on standing vertebral X-rays.[1,2] It is classified into five main types: idiopathic, congenital, syndromic, compensatory, and neuromuscular.[3]

Neuromuscular diseases encompass a variety of conditions affecting either the motor neuron or the peripheral nervous system.[4] Central nervous system (CNS) involvement is not observed in neuromuscular diseases. Scoliosis frequently develops as a complication of neuromuscular diseases, often progressing and necessitating surgical intervention.[1]

Surgical intervention for scoliosis not only halts the progression of cardiopulmonary and neurological decline but also enhances cosmetic appearance. Effective perioperative care involves thorough preoperative preparation, meticulous intraoperative anesthesia management, and vigilant postoperative monitoring. Assessing postoperative medical complications and mortality rates is crucial for evaluating surgical outcomes. With complication rates ranging from 14% to 44%, understanding potential risk factors before surgery and implementing preventive measures are essential.[5,6]

Although complications can arise in spinal fusion surgery for all types of scoliosis, they are more frequent during and after the procedure in cases of neuromuscular scoliosis.[7,8]

Pulmonary and cardiovascular complications are prevalent among individuals with neuromuscular diseases, including unclassifiable lung conditions, pulmonary collapse, insufficiency, chronic respiratory failure, and the need for ventilator support. Cardiovascular issues such as cardiomyopathy, hypotension, and tachycardia are also common. Given these underlying health conditions and associated comorbidities, patients with neuromuscular scoliosis are deemed to be at a heightened risk for postoperative complications.[9,10]

Due to these characteristics, patients with neuromuscular scoliosis represent a unique population requiring special considerations for anesthesia.

This retrospective study aims to explore the preoperative charac-

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teristics, anesthesia protocols, as well as intra- and postoperative complications and associated conditions in patients who underwent surgery for neuromuscular scoliosis at our hospital.

2. Materials And Methods

All patients who underwent surgery with a diagnosis of congenital neuroscoliosis and whose file information was accessible were included in the study, thus a power analysis was not performed.

Inclusion criteria for the study were having undergone surgery for congenital neuroscoliosis. Exclusion criteria included having a psychiatric diagnosis and the inability to access post-operative follow-up records.

After receiving approval from the ethics committee of our hospital, this study conducted a retrospective review of patient files from individuals who underwent surgery for neuromuscular scoliosis at Adana city Hospital between 2017 and 2022. A total of 26 patient files were analyzed.

Patient parameters including age (years), gender (female (F), male (M)), weight (kg), presence of neuromuscular disease, concomitant cardiovascular and respiratory conditions, as well as other systemic anomalies and diseases, spirometry findings (FEV1, FVC, FEV1/FVC), nutritional status (total protein, albumin), pre-operative hemoglobin (Hg) and hematocrit (Htc) levels, Cobb angle index, angle direction, type of surgical approach (anterior or posterior), muscle relaxants utilized, additional dosage requirements, operation duration, intraoperative bleeding volume (ml), transfusion volume (ml), and intraoperative complications were documented. Additionally post-operatively, we recorded hemoglobin (Hg) and hematocrit (Htc) levels, admission to the intensive care unit (extubated or intubated), length of stay in the intensive care unit (in days, greater or less than 72 hours), and any other postoperative complications were recorded.

We investigated whether there was any link between these data collected from patients.

2.1. Statistical analyses

We conducted data analysis using the SPSS for Windows 11.5 software package. The Shapiro-Wilk test determined the distribution of continuous variables' proximity to normality. Descriptive statistics were presented as mean ± standard deviation or median (minimum - maximum). We assessed differences between groups using Student's t-test for means and the Mann-Whitney U test for median values. Nominal variables were analyzed using Fisher's Chi-Square test with Fisher's exact test. Spearman's correlation test determined significant correlations between continuous variables. Results were deemed statistically significant for $p<0.05$

Table 1

Demographic and operative data

Frequency	n	Mean	Std. Deviation	Median	Minimum	Maximum
Age	26	14,62	6,42	13,00	9,00	40,00
Weight	26	39,38	9,86	36,50	26,00	56,00
FEV1	22	66,00	13,86	61,50	47,00	90,00
FVC	22	71,68	16,23	66,00	49,00	101,00
FEV1/FVC	22	92,18	4,70	92,00	78,00	103,00
TPR	26	6,05	1,12	6,01	3,60	8,40
ALB	26	3,71	0,79	4,00	2,20	4,80
PRE Hg	26	12,80	1,20	12,60	10,60	15,00
POST Hg	26	9,60	0,99	9,50	7,50	12,00
PRE Htc	26	37,58	3,85	37,30	32,00	43,00
POST Htc	26	28,88	3,13	29,00	21,00	35,00
Lymphocyte Count	26	2,03	0,91	1,70	1,10	5,00
Curvature Level	26	12,92	2,42	13,00	8,00	18,00
COBB	26	73,73	26,37	72,50	19,00	120,00
Blood Loss	26	1526,92	1691,64	1150,00	450,00	9500,00
Transfusion Volume	26	886,54	390,01	725,00	300,00	1800,00
Operation Duration	26	234,81	51,04	212,50	170,00	330,00
Intensive Care Admission	26	0,80	0,91	0,00	0,00	2,00
Duration of Stay in Intensive Care	26	1,19	1,55	0,00	0,00	5,00
Duration of Hospitalization	26	11,31	3,44	5,00	5,00	20,00

3. Results

Demographic and operative data of the patients are shown in Table 1. In this table, 9 of the patients were male and 17 were female.

Table 2

Patients' history and perioperative data

		Frequency
NM diseases	• 0	1
	• CP	8
	• Duchenne Muscular Dystrophy	1
	• Fa	1
	• Amk	1
	• Nf Type-1	8
	• Nf Type-2	1
	• Neurogenic Bladder	1
	• Polio	3
	• SMS Type-2	1
	• Total	26
Other		
	• 0	14
	• Asthma	1
	• DM Type-1	1
	• Epilepsy	1
	• Kyphosis	3
	• Cystic Fib	1
	• Lymphamgioma	1
	• Meningomyelocele	2
	• Pev	2
	• Total	26
Area	Ctl	3
	Tl	23
	Total	26
Direction	L	19
	R	7
	Total	26
Approach	A	1
	P	25
	Total	26
Intraoperative Comp.	Absent	25
	Present	1
	Total	26
Postoperative Comp.	Absent	25
	Present	1
	Total	26
Intensive Care Unit stay > 72 hours	Absent	22
	Present	4
	Total	26

When examining the correlation between preoperative and intraoperative factors and admission to the intensive care unit (ICU), length of ICU stay, and overall hospitalization duration, we found that the likelihood of ICU admission rose with increased curvature levels (p=0.034). Additionally, both the likelihood of ICU admission (p=0.045) and the duration of ICU stay (p=0.019) increased with higher amounts of transfused blood. No significant correlation was observed between other variables and ICU admissions, ICU length of stay, or overall hospitalization duration (p>0.05). (Table 3)

Table 3

Patient characteristics and laboratory findings

		Sperman's rho		
		Intensive Care Admission	Duration of Stay in Intensive Care	Duration of stay in hospital
AGE	r	,181	,187	,030
	p	,375	,359	,885
	n	26	26	26
FEV1	r	,157	,280	,197
	p	,485	,207	,380
	n	22	22	22
FVC	r	,132	,232	,291
	p	,558	,299	,190
	n	22	22	22
FEV1/FVC	r	,145	,221	-,353
	p	,519	,323	,107
	n	22	22	22
PRE Hg	r	-,265	-,208	-,98
	p	,190	,309	,633
	n	26	26	26
PRE Htc	r	-,161	-,093	-,013
	p	,432	,650	,948
	n	26	26	26
Lymphocyte Count	r	,049	,033	-,105
	p	,812	,874	,608
	n	26	26	26
Curvature Level	r	,418	,338	,078
	p	,034	,092	,706
	n	26	26	26
COBB	r	,306	,356	,221
	p	,129	,104	,277
	n	26	26	26
POST Hg	r	-,351	-,319	-,275
	p	,078	,112	173
	n	26	26	26
POST Htc	r	-,101	-,135	-,250
	p	,624	,511	,218
	n	26	26	26
Blood Loss	r	,230	,290	,273
	p	,257	,151	,178
	n	26	26	26
Transfusion Volume	r	,396	,457	,142
	p	,045	,019	,489
	n	26	26	26
Operation Duration	r	,139	,234	,312
	p	,497	,251	,121
	n	26	26	26

When examining variables in relation to postoperative complications, it was found that the levels of FEV1 (p=0.13) and FVC (p=0.003) were higher in the group experiencing complications compared to those without complications. Additionally, when comparing patients who spent more than 72 hours in the intensive care unit (ICU) with those who did not, it was noted that the postoperative hematocrit (htc) level was lower in the former group (p=0.014).

When analyzing variables potentially affecting the length of stay in the intensive care unit (ICU) and overall hospital stay, it was discovered that the presence of comorbidities ($p > 0.05$) and a Cobb angle greater than 90 degrees were not statistically significant ($p > 0.05$).

As the Cobb angle increased, several factors were affected: the duration of the operation was extended ($p < 0.05$), there was an increase in blood loss ($p = 0.012$), and more blood transfusions were required ($p = 0.32$). Furthermore, there was a correlation between increasing age and the amount of blood transfused ($p = 0.035$).

4. Discussion

In our cohort of 26 patients with neuromuscular disease (NMD), we observed a correlation between increased curvature levels and higher rates of ICU admission. Additionally, as the amount of blood transfusion increased, both the likelihood of ICU admission and the length of ICU stay also increased.

Scoliosis associated with neuromuscular diseases is often progressive.[1] Surgical treatment of scoliosis prevents progression of both cardiopulmonary and neurologic findings.[5] Because of these features, scoliosis requires surgical treatment. However, considering the underlying disease and comorbidities, patients with neuromuscular scoliosis are a special patient group in terms of anesthesia and various complications may develop.

In patients undergoing surgery for idiopathic scoliosis, the major complication rate is 8.6%, with a mortality rate of 0.03% and a pseudoarthrosis rate of 5%.[6] When comparing pediatric and adult patients with idiopathic scoliosis, pediatric patients have lower rates of total complications (14.9%-25.1%) and mortality (0.17%-0.40%) than adult patients.[9]

The mean age of patients undergoing scoliosis surgery ranged from 16 to 47 years, with an average Cobb angle of 40°. Intraoperative bleeding averaged 1038 cc, while the preoperative FEV1/FVC ratio was 89.5. Patients stayed in the hospital for an average of 19 days, with a mean duration of 0.86 days in the intensive care unit. Intraoperative mortality was 1%, with postoperative mortality at 0.05%, and postoperative complications were observed in 7% of cases.[8]

Studies have indicated that in patients with NMD undergoing scoliosis surgery, the mean Cobb angle ranges from 44° to 79.3°. Intraoperative bleeding averages between 1641 and 3221 cc, with patients typically staying in the hospital for 9.2 to 19 days and spending 2 to 3 days in the ICU on average. The mortality rate is around 6.5%, and the incidence of postoperative complications is approximately 15%.[3,5,7]

Among patients with NMD, pulmonary complications stand out as the most frequent preoperative issue, followed by cardiac complications. Pneumothorax emerges as the leading major pulmonary complication.[7] However, in our study, we observed no instances of either pulmonary or cardiac complications. Only one patient experienced bladder perforation.

The primary postoperative complications predominantly revolve around pulmonary issues. These complications entail prolonged atelectasis, intubation exceeding 48 hours, pneumonia, and pneumothorax.[5] Following closely, the second most frequent complication is wound infection, predominantly superficial. Neurological complications rank third in frequency. Additionally, cardiovascular complications such as rod fracture, loosening, pseudoarthrosis, and screw loosening are also observed.[5]

Comparing patients with NMD to those with idiopathic conditions, studies indicate higher total hospital costs, increased comorbidity rates, longer hospital stays, elevated rates of wound site infection, major complications, mortality, pseudoarthrosis, and respiratory failure among patients with NMD.[6]

In a study comprising 194 cases, Weis et al. found no significant correlation between postoperative complications and various factors, including age, gender, Cobb angle, intraoperative and postoperative bleeding, perioperative and postoperative hemoglobin levels, instrumentation level, blood transfusion volume, and preoperative RFT (Respiratory Function Tests) values.[6]

Mohammed et al. further noted in their study of 175 patients with NMD that the group experiencing postoperative complications had longer operation times (419 min vs. 373 min) and higher blood loss (1930 ml vs. 1047 ml) compared to those without complications. Additionally, they found no correlation between postoperative complications and factors such as the surgical approach direction (anterior or posterior), platelet count, white blood cell count, and gender.[5]

In our study, we found that the FEV1/FVC ratio was significantly higher in the group experiencing postoperative complications compared to those without complications. Furthermore, there was a notable increase in the number of intensive care unit admissions and the duration of stay in the intensive care unit as the level of instrumentation and the volume of blood transfused increased.

There was no statistically significant difference observed between anterior and posterior approaches concerning postoperative complications and the duration of intensive care unit stays. In a study involving 126 cases, Hod-Feins et al. noted a lower complication rate with the posterior approach compared to the anterior approach, along with a shorter duration of stay in the intensive care unit. However, they found no association between the Cobb angle, level of instrumentation, and postoperative complications.[8]

When comparing patients who remained in the intensive care unit for more than 72 hours with those who stayed for less than 72 hours, it was found that the former group had significantly lower postoperative hematocrit (HTC) values. Udink et al. noted in their study of 46 NMD patients that 15% required mechanical ventilation for over 72 hours. Interestingly, age and gender showed no association with prolonged mechanical ventilation. However, patients with less than 72 hours of ventilation exhibited lower FEV1 and VC.[3]

While there was a notable correlation between the Cobb angle and factors such as operation time, blood loss, and blood volume, no significant difference in complications was observed between patients with a Cobb angle above and below 90°. We attribute this to the experience of our surgical team. Working with a seasoned team, we believe that preoperative and postoperative complications are not necessarily tied to the Cobb angle. In a study by MODI et al. involving 50 NMD patients, it was found that those with a Cobb angle above 90° exhibited a higher complication rate, longer operation times, and 68% of them experienced at least one major or minor complication. Additionally, they reported two fatalities: one due to hypovolemic shock and the other due to cardiac arrest.[10]

No statistically significant difference was found between the groups with and without comorbidities. In a study conducted by Patil et al., it was observed that the risk of complications was 1.53 times higher in patients with preoperative comorbidities compared to those without. Similarly, Sarıcaoğlu et al. reported that patients who experienced complications had at least one comorbidity.[4]

5. Conclusion

Anesthesia protocols for surgical procedures related to scoliosis involve considerations that impact various bodily systems, particularly the pulmonary and cardiovascular systems.

It has been concluded that a comprehensive preoperative assessment is crucial, as it can offer valuable insights into anesthesia management both before and after surgery for scoliosis. Therefore, conducting a detailed preoperative evaluation is essential for patients undergoing these procedures.

Statement of ethics

Ethical permission was obtained from the Adana City Training and Research Hospital Clinical / Human Research Ethics Committee for this study date on 25.07, 2024, and decision number 81 and Helsinki Declaration rules were followed to conduct this study.

Source of Finance

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

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

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

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