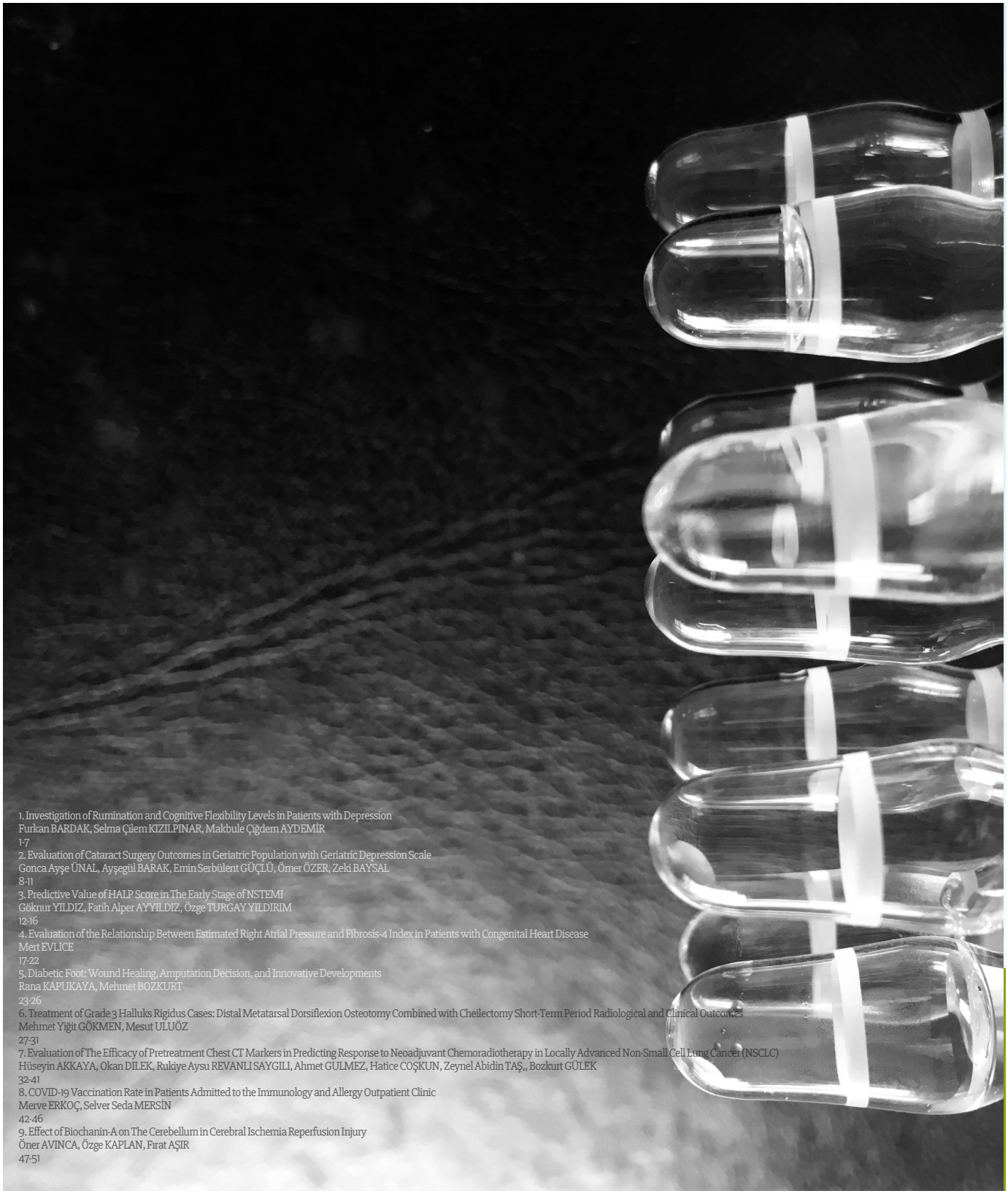
2024 MARCH VOL 7 ISSUE 1

ÇUKUROVA

ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ



1. Investigation of Rumination and Cognitive Flexibility Levels in Patients with Depression
Furkan BARDAK, Selma Çilem KIZILPINAR, Makbule Çiğdem AYDEMİR
1-7
2. Evaluation of Cataract Surgery Outcomes in Geriatric Population with Geriatric Depression Scale
Gonca Ayşe ÜNAL, Ayşegül BARAK, Emin Serbülent GÜÇLÜ, Ömer ÖZER, Zeki BAYSAL
8-11
3. Predictive Value of HALP Score in The Early Stage of NSTEMI
Göknur YILDIZ, Fatih Alper AYYILDIZ, Özge TURGAY YILDIRIM
12-16
4. Evaluation of the Relationship Between Estimated Right Atrial Pressure and Fibrosis-4 Index in Patients with Congenital Heart Disease
Mert EVLICE
17-22
5. Diabetic Foot: Wound Healing, Amputation Decision, and Innovative Developments
Rana KAPUKAYA, Mehmet BOZKURT
23-26
6. Treatment of Grade 3 Halluks Rigidus Cases: Distal Metatarsal Dorsiflexion Osteotomy Combined with Cheilectomy Short-Term Period Radiological and Clinical Outcomes
Mehmet Yiğit GÖKMEN, Mesut ULUÖZ
27-31
7. Evaluation of The Efficacy of Pretreatment Chest CT Markers in Predicting Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)
Hüseyin AKKAYA, Okan DILEK, Rukiye Aysu REVANLI SAYGILI, Ahmet GULMEZ, Hatice COŞKUN, Zeynel Abidin TAŞ,, Bozkurt GÜLEK
32-41
8. COVID-19 Vaccination Rate in Patients Admitted to the Immunology and Allergy Outpatient Clinic
Merve ERKOÇ, Selver Seda MERSİN
42-46
9. Effect of Biochanin-A on The Cerebellum in Cerebral Ischemia Reperfusion Injury
Öner AVINCA, Özge KAPLAN, Fırat AŞIR
47-51

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA

ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

ABSTRACTED & INDEXED

TRDizin
CrossRef
Index Copernicus Master Journal List
Scilit
Türk-Medline
BASE
Google Scholar
ASOS Indeks
Türkiye Atıf Dizini

AIM

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

SCOPE

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

CORRESPONDENCE & CONTACT

Selahattin Eyyubi Mahallesi, Şht. Jnd. Er Gökhan Yılmaz Cd. No:142, 01240 Yüreğir/Adana
+905317936241
anestezidergisi@gmail.com
merthan.tunay@saglik.gov.tr
https://dergipark.org.tr/jocass

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

ETHICAL PRINCIPLES & PUBLICATION POLICY I

Scientific Responsibility

In terms of scientific publishing standards, the articles to be submitted should be prepared in accordance with the criteria of the International Medical Journal Editors Board (ICMJE), Publication Ethics Committee (COPE).
https://publicationethics.org/files/Full_set_of_flowcharts_Turkey_2017%20%281%29.pdf
http://www.icmje.org/recommendations/browse/roles-and-responsibilities/responsibilities-in-the-submission-and-peer-peview-process.html
• The articles to be submitted must comply with research and publication ethics. The responsibility of the articles belongs to their authors.
• Articles should not have been published anywhere before and / or should not be in the evaluation process for publication.
• In order for the evaluation process to begin, the articles must be submitted with the Copyright Transfer Form signed by all authors. For author ranking, the signature order in the Copyright Transfer Form is taken into consideration.
• Corresponding author bears the responsibility of the final version of the article on behalf of all authors.

Ethical Responsibility

• Compliance with the Helsinki Declaration Principles (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) is sought in all studies involving the element of "Human". In such studies, the authors should state that they carried out the study in accordance with these principles in the MATERIAL AND METHODS section, and that they received approval from the ethics committees of their institutions and "informed consent" from the people who participated in the study.
• If the item "Animal" is used in the study, the authors should be informed in the MATERIAL AND METHODS section of the Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use- of-laboratory-animals.pdf), they should state that they protect animal rights in their work and that they get approval from the ethics committees of their institutions.
• In case presentations, "informed consent" should be obtained from the patients.
• Ethics committee approval information should be stated in the MATERIAL and METHODS section, together with the name, approval date and number of the committee.
• 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.

1. Authors

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

a. Predatory or Fake Journals

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

2. Journals

a. security

Manuscripts submitted to journals are privileged communications that are the private, confidential property of the author, and authors can be harmed by premature disclosure of any or all the details of a manuscript.
For this reason, editors should not share with anyone other than the authors and reviewers whether it has been handled and reviewed, its content and status in the review process, including the reviewers' critique and eventual fate. Requests from third parties to use reviews in manuscripts and legal proceedings should be politely refused, and editors should do their best not to provide such confidential material as subpoenas.
Editors should also make it clear that the reviewers must keep the manuscripts, related materials, and information they contain strictly confidential.
Reviewers and editorial staff should not publicly discuss the author's work, and reviewers should not endorse the ideas of the authors prior to publication. Reviewers should not keep the article for their personal use and should destroy the hard copies of the articles and delete the soft copies after submitting their reviews.
When an article is rejected, it is best practice for journals to delete copies from their editorial systems unless local regulations require retention.
Journals that maintain copies of rejected manuscripts should disclose this practice in the Authors' Notice.
When an article is published, journals should retain copies of the original submission, review, revision, and correspondence for at least three years, and possibly permanently, depending on local regulations, to answer future questions about the work.
Editors should not publish reviewers' comments without the permission of reviewers and authors. If journal policy will protect authors against the reviewer's identity and comments are not signed, that identity should not be disclosed to the author or others without the express written consent of the reviewers.
Confidentiality may need to be breached if fraud or alleged fraud is present, but editors notify authors or reviewers of their willingness to do so, and confidentiality should be honored otherwise.

b. Timing

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

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

ETHICAL PRINCIPLES & PUBLICATION POLICY II

c. Peer Review

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

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

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

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

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

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

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

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

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

d. Integrity

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

e. Journal Metrics

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

3. Reviewers

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

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

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

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

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

PLAGIARISM POLICY

The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" are committed to publishing only original material, i.e., material that has neither been published elsewhere, nor is under review elsewhere.
The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" uses software to detect instances of overlapping and similar text in submitted manuscripts: Manuscripts in which plagiarism or textual borrowings are found without reference to the original source are rejected by the editorial board for publication in the journal.

Plagiarism before publication

The journal "Çukurova Anestezi ve Cerrahi Bilimler Dergisi" will judge any case of plagiarism on its own merits. If plagiarism is detected, either by the editors, peer reviewers or editorial staff at any stage before publication of a manuscript - before or after acceptance, during editing or at page proof stage, we will alert the author(s), asking her or him to either rewrite the text or quote the text exactly and to cite the original source. If the plagiarism is extensive - that is, if at least 25% of the original submission is plagiarized - the article may be rejected and the author's institution/employer notified.

Policy of checking for plagiarism

The manuscripts in which plagiarism is detected are handled based on the extent of plagiarism present in the manuscript: if < 25% plagiarism – the manuscript is immediately sent back to the authors for content revision, and if > 25% plagiarism – the manuscript is rejected without editorial review. The authors are advised to revise the plagiarized parts of the manuscript and resubmit it as a fresh manuscript. The percentage of plagiarism is calculated by software and also assessed manually.

Plagiarism after publication

If plagiarism is detected after publication, the Journal will conduct an investigation. If plagiarism is found, the journal editorial office will contact the author's institute and funding agencies. The paper containing the plagiarism will be marked on each page of the PDF. Depending on the extent of the plagiarism, the paper may also be formally retracted.

Recommendations for avoiding plagiarism

Use quotation marks around words taken verbatim from a source Change no part of quotation within the context of the sentence Use single marks for a quotation within a quotation Use ellipses (a space and three periods) for a part of the quotation omitted. Use brackets around added words Limit the use of direct quotes
Attempt to paraphrase the information, or summarize the information derived from a variety of sources using own words.
Authors are responsible for obtaining copyright permission for reproducing illustrations, tables, figures taken from other authors and/or source. Permission must be placed at the foot of each figure.

Self-Plagiarism

Some authors have written several chapters for several different books that are changed only slightly. Each manuscript is copyrighted when published. Because the author no longer owns the rights to these words, one should not plagiarize them. Most editors and reviewers would argue that self-plagiarism is unethical. Thus, an author cannot copy one's own material for a new manuscript without permission of the copyright holder. Alternatives include using quotes around short phrases of own work and citing appropriate references.

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

OPEN ACCESS POLICY

Çukurova Anestezi ve Cerrahi Bilimler Dergisi adheres to the Budapest Open Access Initiative and defines its Open Access policy according to the definition developed in the original BOAI: By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

1. On policy

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

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

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

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

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

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

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

WRITING RULES

PLEASE READ THE SPELLING RULES AND PUBLICATION PRINCIPLES BEFORE SUBMITTING YOUR ARTICLE.

Please read the spelling rules and publication principles before submitting your article.
This journal embraces open publishing and access policies.
All articles are offered under a CC license and are openly accessible. Authors must agree to the terms of open access.
Cover Page: The title should be simple and understandable (in Turkish and English). Name, surname and title of all authors, the name and city of the institution they work for should be included on this page. The name, address, telephone, fax, mobile phone and e-mail information of the author should also be added to this page.
On the first page of the article file, only the author information and, if applicable, the related notes should be found on the first page of the article.
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
References
The authors themselves are responsible for the accuracy of the resources.
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.
Journal names should be shortened according to Pubmed.
Authors are responsible for the correctness of references and spelling.
Manuscripts and punctuation marks must comply with the following examples.
The source is a magazine; The author should be written in full capitalization, and the first name should be written as first letter and larger. Title of article. The journal is abbreviated to Index Medicus. Year: Volume: First page number-Last page number
If the source is a book; Name (s) of the surname of the author (s). The name of the book. What is the pressure? Publication Place: Printing House, Publication Year.
If a chapter from the book was used as a source;Name (s) of the surname of the chapter author (s). Section title. The name of the book. What is the pressure? (First name and last name (s) of ed and Eds. Editor (s): First page number-last page number of the section. Printing place, Publisher, Year of printing.
If the website is shown as source; The name of the Web site. (accessed date)
The source thesis is; First name of the author's surname. Title of the thesis (thesis). Name of the city, University name (if university), Year.
Tables:
1. Tables should be written on a separate page with a single line spacing.
2. Each table should have number and descriptive information above it.
3. If abbreviations are given in the table, these abbreviations can be defined as subtitles under the table and alphabetical order.
4. When previously printed or electronically published tables are used, written permission must be obtained from both the author and the printer and this must be sent to the editor of the journal by fax or mail.
5. Transverse and longitudinal lines should not be used in the table, only a straight line should be drawn at the top and bottom.
6. Tables should not be repeated in the text.
7. Tables should not be placed in writing.
8. Tables should be in the file to which each post is sent to a table.
Figure Graphic Pictures and Subtitles:
1. Subtitles should be written on a separate page with two lines spaced apart.
2. Numbered according to the order in the text and abbreviations in figures, graphics and pictures, abbreviations should be placed in the alphabetical order below the subtitle.
3. Tables, figures and graphics should not be placed in the writing.
4. Magnification ratio and staining technique should be explained in microscopic pictures.
5. When using previously printed or electronically published figures, graphics and illustrations, written permission must be obtained from both the author and the printer, and should be sent to the editor of the journal by fax or post.
6. Written permission must be obtained when using the images of the persons to be recognized.
7. The explanations of the figures should be written at the end of the file to which the manuscript is sent.
8. Table, figure and graphs should be mentioned in the text.
9. The pictures / photos should be colored, the details should be clearly visible and clear.
10. Figures, pictures / photos are separate. jpg file should be added to the system.
11. Image and photo files should not be less than 100 pixel / inch, 8 cm wide and 300dpi.

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

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

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

ÇUKUROVA
ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

REVIEWERS
VOL 6 ISSUE 3

Abdullah DALGIC
İzmir Bozyaka Eğitim Ve Araştırma Hastanesi KBB Kliniği
Abidin SEHİTOGULLARI
Sakarya Üniversitesi Tıp Fakültesi
Ahmet Gökhan SARITAŞ
Çukurova Üniversitesi, Tıp Fakültesi
Ahmet Rıza ŞAHİN
Sağlık Bilimleri Üniversitesi, Adana Şehir Sağlık Uygulama Ve Araştırma Merkezi, Dahili Tıp Bilimleri Bölümü
Ahmet Umut YUVACI
İstanbul Florence Nightingale Hastanesi
Ali ALEMDAR
Genel Cerrahi Anabilim Dalı
Aykağan COŞGUNARSLAN
Oral and Maxillofacial Radiology, Erciyes University
Bahriye ATMIŞ
Çukurova Üniversitesi
Bekir Serhat YİLDİZ
Celâl Bayar Üniversitesi
Belgin USTA GÜÇ
Adana Şehir Sağlık Uygulama Ve Araştırma Merkezi
Bilal Olcay PEKER
İzmir Atatürk Eğitim Ve Araştırma Hastanesi
Burhan Fatih KOÇYİĞİT
Kahramanmaraş Sütçü İmam Üniversitesi, Tip Fakültesi
Demet LAFLI TUNAY
Çukurova Üniversitesi Tıp Fakültesi, Anesteziyoloji Ve Reanimasyon A.D.
Ebubekir GÜNDEŞ
Gazi Yaşargil Eğitim Ve Araştırma Hastanesi
Doğan ATAN
Lokman Hekim Üniversitesi
Duygu TECER
Şanlıurfa Mehmet Akif İnan Eğitim Araştırma Hastanesi
Ebru BİRİCİK
Çukurova University
Eda YILDIZHAN
Dicle Üniversitesi
Emin Serbülent GÜÇLÜ
Mersin Şehir Eğitim Ve Araştırma Hastanesi
Erdal KARAGÜLLE
Başkent Üniversitesi
Erdinç NAYİR
Mersin Üniversitesi
Erdoğan ÖZGÜR
Erol ÖTEN
Amasya Üniversitesi Sabuncuoğlu Şerafeddin EAH Fiziksel Tıp Ve Rehabilitasyon Kliniği, Amasya
Eslem İNCE YILMAZ
Kudret International Hospital.
Ethem ÜNAL
SBÜ Sancaktepe EAH Genel Cerrahi Kliniği
Evren KARAALİ
Sağlık Bilimleri Üniversitesi, Adana Şehir Sağlık Uygulama Ve Araştırma Merkezi
Eyüpcan POLAT
Fatih TAŞ
Siirt Üniversitesi, Tip Fakültesi
Fatih GOKALP
Hatay Mustafa Kemal Üniversitesi
Fesih OK
Siirt Üniversitesi
Fırat ULUTATAR
Çukurova Üniversitesi, Tıp Fakültesi
Firdevs AŞANTOĞROL
Gaziantep Üniversitesi
Gökhan KURAN
Sağlık Bilimleri Üniversitesi
Gökhan ÇAVUŞ
Sağlık Bilimleri Üniversitesi, Adana Şehir Sağlık Uygulama Ve Araştırma Merkezi
Gönül AKDAĞ
Kütahya Sağlık Bilimleri Üniversitesi
Güzin ÖZDEN
Adana Şehir Hastanesi
Halit FİDANCI
Adana Şehir Hastanesi
Kutay DEMİRKAN
Hacettepe Üniversitesi
Mehmet ÖZGEYİK
Eskişehir City Hospital
Merve TOKOCİN
SBÜ Bağcılar Eğitim Ve Araştırma
Nagehan ERDOĞMUŞ KÜÇÜKCAN
Sağlık Bakanlığı
Nur YÜCEL EKİCİ
Adana Şehir Eğitim Araştırma Hastanesi
Onur Olgaç KARAGÜLLE
İstanbul Eğitim Ve Araştırma Hastanesi
Onur Volkan YARAN
Bayburt Devlet Hastanesi
Orkut GÜÇLÜ
Trakya Üniversitesi
Orçun ALTUNÖREN
Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Department of Nephrology
Osman CİLOGLU
Adana Şehir Eğitim Araştırma Hastanesi
Pelin DURU ÇETİNKAYA
Çukurova Üniversitesi, Tip Fakültesi, Dahili Tip Bilimleri Bölümü, Göğüs Hastalıkları Anabilim Dalı
Sait YEŞİLLİK
Sağlık Bilimleri Üniversitesi, Gülhane Eğitim Ve Araştırma Hastanesi, İç Hastalıkları Ana Bilim Dalı, Allerji Ve İmmunoloji Bilim Dalı
Sare Gülfem ÖZLÜ
Ankara Yıldırım Beyazıt Üniversitesi, Ankara Şehir Hastanesi, Çocuk Nefroloji Kliniği
Sema YÜKSEKDAĞ
Ümraniye Eğitim Ve Araştırma Hastanesi
Sevgin TANER
Ege Üniversitesi Tıp Fakültesi, Çocuk Sağlığı Ve Hastalıkları Ana Bilim Dalı, Çocuk Nefroloji
Sezgin ZEREN
Kütahya Sağlık Bilimleri Üniversitesi
Süreyya TALAY
Ankara 29 Mayıs Devlet Hastanesi
Tolga KÖŞECİ
University Of Health Sciences, Adana Numune Health Research Center
Tülay ŞAHİN
İstanbul Şişli Hamidiye Etfal Sağlık Uygulama Ve Araştırma Merkezi
Çağatay KÜÇÜKBİNGÖZ
Sağlık Bilimleri Üniversitesi, Adana Şehir Sağlık Uygulama Ve Araştırma Merkezi, Cerrahi Tip Bilimleri Bölümü, Anesteziyoloji Anabilim Dalı
Ömer ÖZER
Niğde Ömer Halisdemir University, School Of Medicine
Özge TURGAY YILDIRIM
Eskişehir Şehir Hastanesi, Kardiyoloji Kliniği
Özlem ÖZMETE
Başkent Üniversitesi
İbrahim TABAKAN
Çukurova University, Faculty of Medicine
İlker ARER
Emsey Hastanesi
İsmail İŞTEMEN
Adana Şehir Eğitim Ve Araştırma Hastanesi, Beyin Cerrahi Kliniği
İsmail KOÇYİĞİT
Erciyes University
İsmail Cem Eray
Çukurova Üniversitesi, Tıp Fakültesi

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

2024 MARCH VOL 7 ISSUE 1

ÇUKUROVA

ANESTEZİ VE CERRAHİ BİLİMLER DERGİSİ

CONTENTS

1. Investigation of Rumination and Cognitive Flexibility Levels in Patients with Depression
Furkan BARDAK, Selma Çilem KIZILPINAR, Makbule Çiğdem AYDEMİR
1-7
2. Evaluation of Cataract Surgery Outcomes in Geriatric Population with Geriatric Depression Scale
Gonca Ayşe ÜNAL, Ayşegül BARAK, Emin Serbülent GÜÇLÜ, Ömer ÖZER, Zeki BAYSAL
8-11
3. Predictive Value of HALP Score in The Early Stage of NSTEMI
Göknur YILDIZ, Fatih Alper AYYILDIZ, Özge TURGAY YILDIRIM
12-16
4. Evaluation of the Relationship Between Estimated Right Atrial Pressure and Fibrosis-4 Index in Patients with Congenital Heart Disease
Mert EVLICE
17-22
5. Diabetic Foot: Wound Healing, Amputation Decision, and Innovative Developments
Rana KAPUKAYA, Mehmet BOZKURT
23-26
6. Treatment of Grade 3 Halluks Rigidus Cases: Distal Metatarsal Dorsiflexion Osteotomy Combined with Cheilectomy Short-Term Period Radiological and Clinical Outcomes
Mehmet Yiğit GÖKMEN, Mesut ULUÖZ
27-31
7. Evaluation of The Efficacy of Pretreatment Chest CT Markers in Predicting Response to Neoadjuvant Chemoradiotherapy in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)
Hüseyin AKKAYA, Okan DILEK, Rukiye Aysu REVANLI SAYGILI, Ahmet GULMEZ, Hatice COŞKUN, Zeynel Abidin TAŞ,, Bozkurt GÜLEK
32-41
8. COVID-19 Vaccination Rate in Patients Admitted to the Immunology and Allergy Outpatient Clinic
Merve ERKOÇ, Selver Seda MERSİN
42-46
9. Effect of Biochanin-A on The Cerebellum in Cerebral Ischemia Reperfusion Injury
Öner AVINCA, Özge KAPLAN, Fırat AŞIR
47-51

E-ISSN: 2667-498X ESTABLISHED IN 2018, PERIOD MARCH JUNE SEPTEMBER DECEMBER, PUBLISHER: MERTHAN TUNAY

Investigation of Rumination and Cognitive Flexibility Levels in Patients with Depression

Furkan Bardak[1], Çilem Kızılpınar[2], Makbule Çiğdem Aydemir[3]

1 Abant İzzet Baysal University, Department of Psychology, Bolu, Türkiye
2 Adana City Training and Research Hospital, Department of Psychiatry, Adana, Türkiye
3 Ankara University Faculty of Health Sciences, Department of Psychiatry, Ankara, Türkiye

Abstract

Aim: Depression is characterized by continuous depressed mood, anhedonia, loss of interest, and cognitive, behavioral, and physical symptoms. Many psychological factors such as individuals' cognitive processes, high neuroticism, low self-esteem have been reported to play important roles in the etiology, exacerbation, persistence, and treatment of depressive mood. The aim of this study is to compare the levels of rumination and cognitive flexibility in a healthy adult group without any mental disorders and adult patients followed up with depression.

Methods: In this cross-sectional case-control study, patients with depression (n=76, 34.1±9.32) and healthy controls (HG) (n=74, 34.5±10.5) were compared. The Sociodemographic Information Form, Beck Depression Inventory, Ruminative Thinking Scale, and the Cognitive Flexibility Inventory were performed to all participants.

Results: The study showed that depressive patients had higher ruminative thought levels and lower cognitive flexibility levels than healthy individuals. In addition, it was found that cognitive flexibility and ruminative thought severity can explain 35% of the variability of depressive symptom severity in the patient group. In the healthy group, ruminative thought severity can explain 9 % of the variability of depressive symptom severity.

Conclusions: The results of the study showed that ruminative thought and cognitive flexibility are important factors when predicting and preventing depression during the premorbid period and are useful when making formulation and determining treatment goals during the treatment. Therefore, interventions to improve cognitive flexibility and rumination are important. The clinicians should add interventions to cognitive flexibility and rumination into their treatment approach.

Keywords: *Depression, Rumination, Cognitive Flexibility*

1. Introduction

Depression is characterized by at least 2 weeks of continuous depressed mood, anhedonia, loss of interest, and cognitive, behavioral, and physical symptoms. It has significant societal, economic, and clinical implications because can cause a wide range of problems like sadness, difficulties in interpersonal relationships, occupational performance, and educational performance, impairment in assessing reality, slowing of psychomotor skills and cognitive processes, limitations in thought content, and a decrease in functionality, as well as deterioration of social and family harmony[1-3]. It was ranked that the prevalence of depressive disorders is 3440 cases per 100.000 people (95% Uncertainty interval 4038.1-5112.4), and 13th among the top 25 leading causes of DALYs (Disability Adjusted Life Years) in 2019 according to Global Burden of the Disease Study[4]. Similarly, it was reported that 322 million people worldwide, and 3,260,647 people in Turkey suffer from depression according to the World Health Organization's report on Depression and Other Mental Disorders[4].

Many psychological risk factors which can be called transdiagnostic factors in general, have been identified in the development of depression, such as high neuroticism, low self-esteem, negative repetitive thinking, cognitive reactivity, rumination, automatic thoughts, dysfunctional attitudes, and thought suppression[5,6]. The cognitive model of depression which suggests focusing on the cognitive content of the person's reactions to events and thoughts has significantly increased the understanding of cognitive processes in major depression[7]. According to the cognitive model, the real world is rebuilt and distorted by the depressed person who has negative and distorted thoughts about oneself, the environment, and the future, this model is also known as Beck's cognitive triad[8]. People who have depression perceive themselves and the environment and the future

Corresponding Author: Furkan Bardak
e-mail: furkanbardak@yahoo.com
Received: 09.10.2023, Accepted: 01.02.2024, Available Online Date: 01.03.2024
Cite this article as: Bardak F, Kızılpınar Ç, Aydemir MÇ. Investigation of Rumination and Cognitive Flexibility Levels in Patients with Depression. J Cukurova Anesth Surg. 2024; 7(1): 1-7. doi:10.36516/jocass.1372677

with a biased perspective, and usually report repetitive negative thoughts about themselves. There is a mutual interaction between distorted thoughts[9]. It was reported that there is a high relationship between the onset, relapse, and symptom severity of depression and cognitive distortions, negative thoughts about oneself, cognitive rigidity, and immature defense styles[10-12]. These results lead researchers to seek a more comprehensive understanding of depression and focus on cognitive processes and the content of depressive cognition.

Rumination is defined as an attempt to make sense of an upsetting event or to solve a problem. It is very common in the general population. But in substance clinically rumination is conceptualized as repetitive thought on unresolved personal goals and concerns and does not help the progress toward the unattained goal[13]. According to the theory of response styles, it is defined as passive, pervasive, and repetitive thinking patterns about emotional symptoms and the causes and consequences of these symptoms[14]. It can also be defined as the experience of being stuck in the head and focusing on the internal state that causes disengage in positive activities, like learning, and enjoying. Typically, ruminators have more focus on the events and passively and less consider their final reactions[15]. When prolonged, frequent, and extreme, rumination is problematic, contributes to anxiety and depression, reduces motivation, contributes to perseveration of negative affective states, leads to procrastination, and reduces direct contact with the world. Rumination has been related to severe and persistent depression[13,16]. Rumination exacerbates depression and other pathological conditions because it causes increased focus and being attached to negative thoughts and memories while trying to make sense of the distressing events, enhancing the content of fatalistic and pessimistic thinking, reducing problem-solving skills, and reducing adaptation to unstable conditions[17]. Just and Alloy[18] revealed in their longitudinal study of the relationship between depression and rumination that rumination is effective in the onset and exacerbation of depressive symptoms, and that depression is more common in people who think ruminatively. Similarly, Mor and Winquist[19] concluded in their meta-analysis that rumination is consistently and strongly associated with depressive symptoms. In addition, it was stated that patients with ruminative thinking have more severe depressive symptoms[16,18,20].

Cognitive flexibility defines the ability to switch thoughts or to be open to different perspectives[21]. Understanding the options that the individual has, considering difficult life experiences as bearable, and modifying cognitions to adapt to new contexts all are elements of cognitive flexibility[22]. Cognitive rigidity which means one's difficulty in switching ways of responding is the opposite of this. Rigidity refers to a mindset that is "all or nothing" according to cognitive behavioral therapy. When faced with difficult situations, cognitively flexible people are confident in their ability to behave effectively, aware of their options in the face of a situation, evaluate, and integrate various relevant sources of information, and can produce several scenarios during this process. These are important steps in making the right decision[23,24]. Cognitive flexibility has been positively related to psychological well-being, interpersonal competence, life satisfaction, and happiness[25-29], and negatively related to the severity of depressive symptoms[22,30]. Similarly, Deveney and Deldin[31] noticed that patients with depression performed worse than healthy controls in cognitive flexibility tasks in the card matching test when the stimuli were negative, according to the Wisconsin Card Sorting Test. It was stated that cognitive rigidity enhances the acceptance of maladaptive beliefs and causes to persist depression[32]. Moreover, cognitive rigidity which means one's difficulty in switching ways of responding has been related to a worse outcome like enhancement of suicide risk. It has been stated that significant relationship between cognitive rigidity and some transdiagnostic factors like perfectionism, compulsive behaviors, and impulsivity[33].

The study was designed to compare the ruminative thinking style and cognitive flexibility level of patients with depression who applied to a psychiatry outpatient clinic and a healthy control group. We believe that our findings may provide us to improve our understanding of the cognitive forms of depression and reorganize our treatment approach.

2. Materials and methods

2.1. Participants and Study Design

The ethical principles and permissions were obtained from The University Clinical Research Ethics Committee (Date: 20/02/2019, with decision number 87). After providing detailed verbal and written information about the study and obtaining written consent, the participants were recruited into the study. Data was collected with the sociodemographic Data form, the Beck Depression Inventory, the Ruminative Thinking Style Scale, and the Cognitive Flexibility Inventory from all of the participants who volunteered to participate in the study.

The Patient group (PG) enrolled 100 patients diagnosed with Major Depression based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) who applied to the Ankara University Faculty of Medicine Psychiatry outpatient clinic between January 2019 and November 2019, or who were currently being followed. 24 participants were excluded from the study because of refusing to participate, difficulty understanding the scale forms, missing or incorrect marking. 74 healthy subjects who were not diagnosed with any psychiatric disorder and met the study criteria were enrolled in the hospital and outpatient clinic. All of the participants aged between 18 and 65, were literate, not receiving any specialized psychotherapy intervention (cognitive behavioral therapy, etc.), has no history of substance abuse or use of any drugs, and had no additional psychiatric diagnosis based on DSM-V that affects their cognitive process (neurological disease, severe physical illness, history of brain trauma, or ECT treatment in the previous 6 months), to be able to give consent to participate the study, were recruited in the study.

2.2. Measurement Tools

Sociodemographic Data Form

Information on demographic variables such as age, gender, marital and working status, education level, and data on various clinical characteristics such as psychiatric history, smoking or alcohol consumption, substance use, and general medical history was obtained from all participants using the Sociodemographic Data Form which was prepared by the researchers.

The Beck Depression Inventory (BDI)

Beck Depression Inventory was developed to measure the severity of depressive symptoms by Beck et al.[34]. It can be evaluated various symptoms of depression, including sadness, hopelessness, somatic symptoms, vegetative symptoms, self-blame, feeling of guilt, fatigue, and loss of appetite with this scale. The test consists of 21 items and the lowest 0 and the highest 63 points can be rated. The cut-off point was determined as 17 points. The Turkish version of the scale has good reliability and validity properties have been stated, with a Cronbach's alpha of $\alpha = 0.80$[35].

The Ruminative Thought Style Questionnaire (RTSQ)

The scale was developed to assess the general rumination tendency as a thought form, considering ruminative thought as a repetitive, uncontrollable, pervasive, and reversible manner of thinking by Brinker and Dozois (36). It consists of 20 items and is rated every item on a 7-point Likert scale (1 = not at all descriptive of me, 7 = describes me very well). İt was not determined cut-off score. Brinker and Dozois developed the original form of the scale. İt has been reported the scale presents good convergent validity with the

Response Style Questionnaire, the Global Rumination Scale, and the Beck Depression Inventory, adequate test-retest reliability and high internal consistency with a Cronbach's alpha of α = 0.94, and internal consistency coefficient was calculated to be 0.92[36]. Karatepe, Yavuz, and Turkcan conducted a Turkish validity and reliability assessment of the scale, with an internal consistency coefficient of 0.91[37].

The Cognitive Flexibility Inventory (CFI)

The inventory was developed to assess people's capacity to produce alternatives, recognize appropriate options, and think rationally in tough situations by Dennis and Vander Wal[22]. It has a 20-item and two-factor structure. The first factor called the Alternatives subscale provides an assessment of people's ability to comprehend that there are alternatives and find solutions in the face of negative situations. The second factor, called Control subscale measures one's adaptability to challenging situations. The questionnaire was designed on a 5-point Likert scale (1= not at all appropriate and 5=completely appropriate). A high score indicates a high level of cognitive flexibility. The Turkish reliability and validity study was carried out by Gülüm and Dağ[38] The internal consistency value was found 0.91 for the Alternative subscale and 0.84 for the Control subscale. Cronbach's alpha coefficients were found to be .89 for the Alternatives subscale, 0.85 for the Control subscale, and .90 for the Total scale.

2.3. Statistical Analysis

It was evaluated whether the continuous variables had normal distribution by the Shapiro-Wilk test. The descriptive statistics of the data like the mean, standard deviation, maximum-minimum values, distributions, and ratios were determined. Independent sample t-test and Mann-Whitney U test were used for comparisons between two groups of continuous variables. Pearson Chi-Square Test was used for comparisons between categorical variables. Pearson correlation analysis was used to examine the relationships between the variables. Linear regression analysis was applied to calculate the effect of the main variables of the study. Statistical analyzes were performed with SPSS 26.0 (SPSS Inc, Chicago, IL, USA) package program and the level of significance was accepted as p<0.05. p<.01, p<.001.

3. Results

In this cross-sectional case-control study, patients with depression (PG, n=76, 34.1±9.32) and healthy controls (HC, n=74, 34.5±10.5) were compared in terms of ruminative thinking styles and cognitive flexibility levels. There was found no statistically significant difference between the two groups in terms of age, gender, working, and marital status (respectively p = .80, .25., 89, 19) The sociodemographic characteristics of the participants are shown in Table 1.

Table 1

Sociodemographic Characteristics of the Patient and Healthy Control Groups

Characteristic	PG (n:76)	HG (n:74)	Statistical Analysis
Age (years)	34.1±9.32 (18-62)	34.5±10.5 (18-62)	t=.-25, pa=.80
S (Female n, %)	52 (68.4%)	44 (59.5%)	x2=1.31, p=.25
Marital status (married n, %)	54 (71.1%)	45 (60.8%)	x2=1.75, p=.19
Working status (unemployed n, %)	45 (59.2%)	43 (58.1%)	x2=.019 p=.89

Note; a= Independent Sample t-Test, x2= Chi Square

PG and HC were compared in terms of RTSQ score and CFI there was a statistically significant difference between the groups (both p<0.05). The PG has a higher ruminative thinking level and a lower cognitive flexibility level than the HC (Table 2).

Table 2

The Comparison Between the Groups in terms of the Ruminative Thought Style Questionnaire score and Cognitive Flexibility Inventory Score

	PG			HG				
	N	Mean	SD	N	Mean	SD	t	p
RTSQ	76	101.8	17.9	74	88.2	10.9	9.02	.00*
CFI	76	62.7	8.1	74	68.9	9.0	-9.46	.00**
Alternatives	76	44,4	7.3	74	49.5	8.5	-8.18	.00**
Control	76	18.6	4.6	74	19.9	5.1	-3.34	.00**

*Note; * Mann Whitney U; ** Independent Sample t Test*

Pearson correlation analysis was performed to examine the relationship between the participants' depressive symptom severity, cognitive flexibility (control, and alternative subscale) ruminative thinking level, and age. It was found a negative relationship between depressive symptom severity and CFI-Alternatives subscale RTSQ score (both p<0.01), and a positive relationship between depressive symptom severity and CFI-Control subscale (p<0.01) for the patients. There was a positive significant relationship between RTSQ and CFI-Control subscale (p<0.01) and a negative significant relationship between RTSQ and CFI-Alternatives subscale (p<0.01). The results were shown in Table 3

Table 3

Correlation between the Patient Group in terms of Various Sociodemografical and Clinical variables

	1	2	3	4	5	6
1-Age						
2-Dep. Sym. Sev. (BDI)		.14	.07	-.06	.13	-.01
3-RTSQ			-.42**	-.40**	.31**	-22**
4-CFI-total				.08	.53**	-.24**
5-CFI-Control					.43**	.82**
6-CFI Alternatives						

*Note; ** p<0,01, Dep Sym. Sev.: Depressive Symptom Severity measured by Beck Depression Inventory, RTSQ: The Ruminative Thought Style Questionnaire, CFI: The Cognitive Flexibility Inventory, CFI-Control: The Cognitive Flexibility Inventory Control Subscale, CFI-Alternatives: The Cognitive Flexibility Inventory Alternatives Subscale*

Table 4

Correlation between the Control Group in terms of Various Sociodemografical and Clinical variables

	1	2	3	4	5	6
1-Age						
2-Dep. Sym. Sev. (BDI)		.11	.03	.00	-.23*	-.04
3-RTSQ			.28**	.13	.13*	.06
4-CFI-total				.37**	.53**	.07
5-CFI-Control					.40**	.83**
6-CFI Alternatives						

*Note; ** p<0,01, Dep Sym. Sev.: Depressive Symptom Severity measured by Beck Depression Inventory, RTSQ: The Ruminative Thought Style Questionnaire, CFI: The Cognitive Flexibility Inventory, CFI-Control: The Cognitive Flexibility Inventory Control Subscale, CFI-Alternatives: The Cognitive Flexibility Inventory Alternatives Subscale.*

It was found a positive relationship between depressive symptom severity and the CFI-Control subscale RTSQ score (both p<0.01), and a positive relationship between the RTSQ and CFI-Control subscale (p<0.01) for the HC. There was a positive significant relationship between RTSQ and CFI-total and CFI control subscale (both p<0.01) The results were shown in Table 4.

In the study, linear regression analysis examined the variables that predicted the depressive symptom levels of the patient group. ANOVA test was performed to examine whether the regression model was significant. According to the results, the model is statistically significant (F (2,75) = 9.23, p <. 001, R^2 =0.35) and the R2 value indicated that 35% of the variability of depressive symptom severity is explained by the BDI and RTSQ. When the regression model was examined, it was observed that RTSQ had a positive and significant effect on depressive symptom severity (t=6.618, p<0.05, β=0.441), and the level of cognitive flexibility had a negative and significant effect (t =-6.34, p<0.05, β=-0.423). The results were shown in Table 5.

Figure 1

The Effect of Ruminative Thought and Cognitive Flexibility Levels on Depressive Symptom Severity

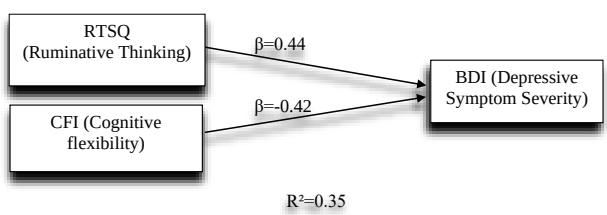


Table 5

Patient Group Linear Regression Analysis Results

	B	SE(B)	B	t	R²	F
CFI	-0.465	0.073	-0.423	-6.34	0.349	39.39
RTSQ	0.224	0.034	0.441	6.62		

NOTE; SE: Standart Error

Similarly, linear regression analysis examined the variables that predicted the depressive symptom levels of the HC. Before the regression analysis, the relationship between the variables was examined and it was observed that there was only a relationship between depressive symptom severity (BDI) and RTSQ score. ANOVA test was performed to examine whether the regression model was significant.

Table 6

Patient Group Linear Regression Analysis Results

	B	SE(B)	B	t	R²	F
Ruminative Thinking	0.043	0.02	0.30	2.68	0.09	0.009

NOTE: SE: Standart Error

According to the results, the model is statistically significant (F (1,73) = 7.2, p<.001, R^2 =.09), and the R2 value indicated that 9% of the variability of depressive symptom severity is explained by the RTSQ. It was observed that RTSQ had a positive and significant effect on depressive symptom severity (t=2.68, p=0, β= 0.30). The results were shown in Table 6.

4. Discussions

Depression is a common disorder that causes severe social, economic, and social consequences in our country and the world and it affects people's lives very seriously. The results of the study show that depressive patients had higher ruminative thought levels and lower cognitive flexibility levels than healthy individuals. There was found a significant and negative relationship between ruminative thought, cognitive flexibility, and depressive symptom severity in the patient group. In the control group, there was a significant negative relationship between only ruminative thought and depressive symptom severity. In addition, it was found that cognitive flexibility and ruminative thought severity can explain 35% of the variability of depressive symptom severity in the patient group. In the healthy group, ruminative thought severity can explain 9 % of the variability of depressive symptom severity. According to the results, it can be said that the cognitive flexibility and ruminative thinking level have had a significant effect on depressive symptom levels in the patient group and the ruminative thought level has a significant effect in the healthy control group. Even if there are not many studies examining the relationship between depressive symptom levels and ruminative thinking in the clinical population the results from the studies are consistent with the present study. It has been shown in two studies conducted in a non-clinical sample that ruminative thought is related to depressive mood[39,40]. It was stated that the level of ruminative thinking contributed to the explanation of depressive symptoms both directly and through negative metacognitive beliefs[40].

The results obtained from the literature review show that healthy individuals with a tendency to ruminative thinking can easily enter a depressive mood, and it increases the severity of the disease in clinical patients diagnosed with depression[41]. There were some explanations for this close relationship between depression and rumination. People who experience depressive moods and are faced with negative life events constantly think about the causes and consequences of the negative events and overthinking causes negative events to remain in the memory constantly and creates negative reactions to the current positive situation. For this reason, individuals under the influence of rumination are more likely to encounter diseases that will turn into emotional disorders such as depression and anxiety. For this reason, ruminators have a high risk for depression and anxiety disorders[42]. Besides, rumination facilitates access to negative cognitions and triggers negative emotional states. Even, for this reason, rumination has been described as an emotional magnifier[13]. The negative thought style is cut down people's problem-solving skills and motivation for problem-solving. It was stated that these situations contribute to the development of depression[14]. Those results lead clinicians to seek advanced treatment for rumination. It was suggested that a lot of therapy approaches like Rumination Focused-Cognitive Behavioral Therapy, Cognitive Bias Modification, Metacognitive Therapy, Mindfulness-Based-Cognitive Behavioral Therapy, cognitive Control Training, and Self Systems Therapy[43].

According to another result of the study, there was a negatively significant relationship between cognitive flexibility levels and depressive symptom levels in the patient group. In other words, the patient who has low cognitive flexibility had higher depressive symptom severity. In the control group, there was no relationship

between cognitive flexibility and the level of depressive symptoms. Similarly in the literature, negative relationships between cognitive flexibility and depressive symptoms were shown in the clinic and non-clinic populations[30,31,44-46]. A similar relationship has also been shown in caregivers of cancer patients[47]. In another study which is used emotional and neutral stimuli; patients with depression spend more time and attention while performing tasks with emotional stimuli have been reported[48]. This may be due to that high cognitive flexibility provides the person's high belief that they can easily solve problems and change their thoughts in a positive way. While cognitive flexibility has been related to individuals producing different perspectives and solutions against current situations, cognitive rigidity has been related to higher vulnerability to tough life events and in the end, the outcome is increased depression risk[46]. With the results and literature review, thinking about the causes and consequences of events deeply, having difficulties in producing alternative solutions, and not being able to control own negative thoughts may cause enlargement of depressive symptom severity and duration for the patient with depression can be said. In the non-clinical population, those excuses cause a negative mood. As a result of our research and the knowledge from previous research, if cognitive rigidity is one of the causes of depression, treatment of this symptom may be prevented the occurrence of major depression can be said.

Therefore, interventions related to cognitive rigidity are important in the approach to patients with depression. Being able to produce alternative solutions without being stuck on the problems and developing their problem-solving skills should be among the treatment goals. Various studies were shown Cognitive Behavioral Therapy is useful for the remediation of cognitive flexibility[49,50], though, Oishi et al.[51] suggested that stress management training on the internet can enhance cognitive flexibility levels. Greenberg et al[52] stated that mindfulness practice is beneficial for reducing cognitive rigidity. But the opposite of those results Johnco et al.[53] said that CBT couldn't provide significant improvement in cognitive flexibility. However, we think that whatever the final result, the clinicians had to use effective technics to improve cognitive rigidity.

The limitations of the study are including the cross-sectional design which reduces the researchers' interpretation of causality, and it provided self-report data from participants which causes them may not to be honest about their ideas, behaviors, and attitudes when filling out the measurement tools. In addition, the drug treatments currently used by the patients were overlooked. This is an important limitation. Additionally, the data cannot be generalized because of made only in a certain period and group and included only a small number of patients with depression. But, it can be said that the patient and control groups are similar in terms of gender, employment status, marital status, and age. Besides, to exclude factors that may affect the test results it has been taken as a condition that they should not have additional medical, neurological, or psychiatric diagnoses and have no individualized psychotherapeutic interventions in the past and present for the participants. These are advantages for our study, considering the effects of the factors on the tests.

In the literature, it was reported that depressive symptoms are related to executive functions, cognitive rigidity, and ruminative thinking[14,22]. Recent studies about rumination have been marked the studies' results may change because of study population features, experiment design, various impairments of cognitive functions, intellectual ability, executive functions, problem-solving abilities, and coping strategies[54,55]. It was not adjusted to these factors in the study and unfortunately, it is a limitation, but Davis and Nolen-Hoeksema[56] stated that there is a direct relationship between ruminative thought and cognitive flexibility and depressive symptoms severity in both patients and non-clinic populations.

5. Conclusions

Depression is a common disorder that causes severe social, economic, and social consequences in our country and the world and it affects people's lives very seriously. The results of the study showed that ruminative thought and cognitive flexibility are important factors for the formulation of patient problems, and for determining treatment goals during the treatment. Therefore, interventions to improve cognitive flexibility and rumination are important. Clinicians should combine interventions to cognitive flexibility and rumination into their treatment approach. These interventions would provide to increase the effectiveness of therapies, make shorter the therapy and treatment duration, and reduce the risk of relapse. We hope that this study and future studies which are carefully designed, large-sample, prospective studies will determine the various transdiagnostic factors in depression and other mental disorders to develop targeted prevention and treatment programs.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by The Ankara University Clinical Research Ethics Committee (Date: 20/02/2019, with decision number 87).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Helvacı Çelik F, Hocaoğlu Ç. Major Depresif Bozukluk' Tanımı, Etyolojisi ve Epidemiyolojisi: Bir Gözden Geçirme. Çağdaş Tıp Dergisi 2016; 6: 51-66. [CrossRef] https://doi.org/10.16899/ctd.03180
2. Oral, M. Majör depresyon tanısı almış kadınlarda kişilerarası ilişkiler terapisi yaklaşımına dayalı grupla sosyal hizmet uygulamasının psikososyal işlevsellik üzerine etkisi. Hacettepe Üniversitesi 2016; Ankara.
3. Irak M, Albayrak EO. Psychometric properties of the expanded version of the inventory of depression and anxiety symptoms in a Turkish population. Psychological Reports 2020; 123:517-545. [CrossRef] https://doi.org/10.1177/0033294118813844
4. World Health Organization. Depression and other common mental disorder 2017. Access Address: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf
5. Ehring T, Watkins E. R. Repetitive negative thinking as a transdiagnostic process. International Journal of Cognitive Therapy 2008; 1: 192-205. [CrossRef] https://doi.org/10.1521/ijct.2008.1.3.192
6. Struijs SY, de Jong, PJ, Jeronimus BF, van der Does W, Riese H, Spinhoven P. Psychological risk factors and the course of depression and anxiety disorders: A review of 15 years NESDA research. Journal of Affective Disorders 2021; 295: 1347-1359. [CrossRef] https://doi.org/10.1016/j.jad.2021.08.086
7. LeMoult J, Gotlib IH. Depression: A cognitive perspective. Clinical psychology review 2019; 69:51-66. [CrossRef] https://doi.org/10.1016/j.cpr.2018.06.008
8. Türkçapar H. Klinik Uygulamalarda Bilişsel-Davranışçı Terapi: Depresyon. 4.Baskı. İstanbul: Epsilon Yayınevi, 2018.
9. Dinç M. Aaron Temkin Beck: Eleştirel düşüncenin peşinden yaratıcı bir psikoterapi kuramına. Bilişsel Davranışçı Psikoterapi ve Araştırmalar Dergisi 2012; 1: 70-76. [CrossRef]

10. Batmaz S, Kocbiyik S, Yalçınkaya-Alkar Ö, Turkcapar M. Cognitive distortions mediate the relationship between defense styles and depression in female outpatients. The European Journal of Psychiatry 2016; 30: 237-247. [CrossRef]
11. Pothier B, Dobson KS, Drapeau M. Investigating the relationship between depression severity and cognitive rigidity through the use of cognitive errors. Archives of Psychiatry and Psychotherapy 2012, 2, 35-40. [CrossRef]
12. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. Annual review of clinical psychology 2010; 6: 285-312. [CrossRef]
https://doi.org/10.1146/annurev.clinpsy.121208.131305
13. Watkins ER. Rumination-focused cognitive-behavioral therapy for depression. New York: Guilford, 2018.
14. Lyubobirsky S, Layous K, Chancellor J, Nelson K. Thinking about rumination: the scholarly contributions and intellectual legacy of Susan Nolen Hoeksema. Annual Review of Clinical Psychology 2015; 11: 1-22. [CrossRef]
https://doi.org/10.1146/annurev-clinpsy-032814-112733
15. Lyubobirsky S, Caldwell ND, Nolen-Hoeksema S. Effects of ruminative and distracting responses to depressed mood on retrieval of autobiographical memories. Journal of Personality and Social Psychology 1998; 75: 166-77. [CrossRef]
https://doi.org/10.1037//0022-3514.75.1.166
16. Nolen-Hoeksema S. Ruminative coping with depression. Heckhausen. J, Dweck CS (Ed.), Motivation and self-regulation across the life span (ss. 237-256). New York: Cambridge University Press 1998.
https://doi.org/10.1017/CBO9780511527869.011
17. Nolen-Hoeksema S. Responses to depression and their effects on the duration of depressive episodes. Journal of Abnormal Psychology 1991; 100: 569-582. [CrossRef]
https://doi.org/10.1037//0021-843X.100.4.569
18. Just N, Alloy LB. The response styles theory of depression: Tests and an extension of the theory. Journal of Abnormal Psycholog 1997; 106: 221-229. [CrossRef]
https://doi.org/10.1037//0021-843X.106.2.221
19. Mor N, Winquist J. Self-focused attention and negative affect: A meta-analysis. Psychological Bulletin 2002; 128: 638-662. [CrossRef]
https://doi.org/10.1037//0033-2909.128.4.638
20. Nolen-Hoeksema S, Morrow J, Fredrickson BL. Response styles and the duration of episodes of depressed mood. Journal of abnormal psychology 1993; 102:20. [CrossRef]
https://doi.org/10.1037//0021-843X.102.1.20
21. Stevens AD. Social problem-solving and cognitive flexibility: Relations to social skills and problem behavior of at-risk young children. (Unpublished PhD Thesis) ProQuest Dissertations and Theses database'den reached 2009.
22. Dennis JP, Vander Wal JS. The Cognitive Flexibility Inventory: Instrument development and estimates of reliability and validity. Cognitive Therapy Research 2010; 34: 241-253. [CrossRef]
https://doi.org/10.1007/s10608-009-9276-4
23. Martin MM, Anderson CM, Thweatt KS. Aggressive communication traits and their relationships with the Cognitive Flexibility Scale and the Communication Flexibility Scale. Journal of Social Behavior and Personality 1998; 13: 531-540. [CrossRef]
24. Martin MM, Anderson CM. The cognitive flexibility scale: Three validity studies. Communication Research Repots 1998; 11: 1-9. [CrossRef]
https://doi.org/10.1080/08934219809367680
25. Cardom RD. The mediating role of cognitive flexibility on the relationship between cross-race interactions and psychological well-being (Doctoral disserta-tion). Retrieved from 2016. [CrossRef]
26. Fu F, Chow A. Traumatic exposure and psychological well-being: The moderating role of cognitive flexibility. Journal of Loss and Trauma 2017, 22(1), 24-35. [CrossRef]
https://doi.org/10.1080/15325024.2016.1161428
27. Asıcı E, İkiz F. A pathway to happiness: Cognitive flexibility. Mehmet Akif Ersoy University Educational Faculty Journal 2015; 1: 191-211. [CrossRef]
28. Rubin R, Martin M. Development of a measure of interpersonal competence. Communication Research Reports 1994; 11:33-44. [CrossRef]
https://doi.org/10.1080/08824099409359938
29. Çikrıkci Ö. The predictive roles of cognitive flexibility and error oriented motivation skills on life satisfaction. International Journal of Eura-sia Social Sciences 2018; 9:717-727. [CrossRef]
30. Yu Y, Yu Y, Lin Y. Anxiety and depression aggravate impulsiveness: the mediating and moderating role of cognitive flexibility. Psychology, Health & Medicine 2020; 25: 25-36. [CrossRef]
https://doi.org/10.1080/13548506.2019.1601748
31. Deveney CM, Deldin PJ. A preliminary investigation of cognitive flexibility for emotional information in major depressive disorder and non-psychiatric controls. Emotion 2006; 6: 429-437. [CrossRef]
https://doi.org/10.1037/1528-3542.6.3.429
32. Moore RG. It's the thought that counts: The role of intentions and meta-awareness in cognitive therapy. Journal of Cognitive Psychotherapy: An International Quarterly 1996; 10:255-269. [CrossRef]
https://doi.org/10.1891/0889-8391.10.4.255
33. Morris L, Mansell W. A systematic review of the relationship between rigidity/flexibility and transdiagnostic cognitive and behavioral processes that maintain psychopathology. Journal of Experimental Psychopathology 2018, 9(3). [CrossRef]
https://doi.org/10.1177/2043808718779431
34. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry 1961; 4:561-571. [CrossRef]
https://doi.org/10.1001/archpsyc.1961.01710120031004
35. Hisli, N. Beck Depresyon Envanteri'nin geçerliliği üzerine bir çalışma. Psikoloji Dergisi 1988; 6:118-122. [CrossRef]
36. Brinker JK, Dozois DJA. Ruminative thought style and depressed mood. Journal of Clinical Psychology 2009; 65:1-19. [CrossRef]
https://doi.org/10.1002/jclp.20542
37. Karatepe HT, Yavuz FK, Turkcan A. Validity and reliability of the Turkish version of the ruminative thought style questionnaire. Klinik Psikofarmakoloji Bülteni 2013; 23: 231-241. [CrossRef]
https://doi.org/10.5455/bcp.20121130122311
38. Gülüm Vİ, Dağ İ. Tekrarlayıcı düşünme ölçeği ve bilişsel esneklik envanterinin Türkçe uyarlaması, geçerliliği ve güvenilirliği. Anatolian Journal of Psychiatry 2012; 13:216-223. [CrossRef]
39. Hong RY. Worry and rumination: Differential associations with anxious and depressive symptoms and coping behavior. Behaviour Research and Therapy 2007; 45: 277-290. [CrossRef]
https://doi.org/10.1016/j.brat.2006.03.006
40. Yılmaz AE. Depresyonun üstbilişsel modeli'nin Türkiye'deki bir üniversite öğrencisi örnekleminde incelenmesi. Türk Psikiyatri Dergisi 2016; 27:100-9. [CrossRef]
41. Takagishi Y, Sakata M, Kitamura T. Influence of rumination and self-efficacy on depression in Japanese undergraduate nursing students. Asian Journal of Social Psychology 2013; 16:163-168. [CrossRef]
https://doi.org/10.1111/ajsp.12000
42. Chen J, Rapee RM, Abbot MJ. Mediators of the relationship between social anxiety and post-event rumination. Journal of Anxiety Disorders 2013; 27:1-8. [CrossRef]
https://doi.org/10.1016/j.janxdis.2012.10.008
43. Watkins ER, Roberts H. Reflecting on rumination: Consequences, causes, mechanisms and treatment of rumination. Behaviour Research and Therapy 2020; 127. [CrossRef]
https://doi.org/10.1016/j.brat.2020.103573
44. Yazar MS, Şenyaşar Meterelliyoz K. Klinik olmayan populasyonda depresif semptomatoloji, bilişsel Esneklik ve umutsuzluk İlişkisinin incelenmesi. Bilişsel Davranışçı Psikoterapi ve Araştırmalar Dergisi 2019; 8:155-163. [CrossRef]
45. Goring HJ, Papageorgiou C. Rumination and worry: Factor analysis of self-report measures in depressed participants. Cognitive Therapy and Research 2008, 32: 554-566. [CrossRef]
https://doi.org/10.1007/s10608-007-9146-x
46. Fresco DM, Rytwinski NK, Craighead LW. Explanatory flexibility and negative life events interact to predict depression symptoms. Journal of Social and Clinical Psychology 2007; 26: 595-608. [CrossRef]
https://doi.org/10.1521/jscp.2007.26.5.595
47. Karabekiroğlu A, Demir EY, Aker S, Kocamanoğlu B, Karabulut GS. Predictors of depression and anxiety among caregivers of hospitalised advanced cancer patients. Singapore Medical Journal 2018; 59:572-577. [CrossRef]
https://doi.org/10.11622/smedj.2018066
48. Murphy FC, Michael A, Sahakian BJ. Emotion modulates cognitive flexibility in patients with major depression. Psychological Medicine 2012; 42:1373-1382. [CrossRef]
https://doi.org/10.1017/S0033291711002418
49. Nazarzadeh RS, Fazeli M, Aval MM, Shourch RM. Effectiveness of cognitive-behavior therapy on cognitive flexibility in perfectionist. Psychology 2015; 6: 1780. [CrossRef]
https://doi.org/10.4236/psych.2015.614174
50. Yasinski C, Hayes AM, Ready CB, Abel A, Görg N, Kuyken W. Processes of change in cognitive behavioral therapy for treatment-resistant depression:

psychological flexibility, rumination, avoidance, and emotional processing. Psychotherapy Research 2020; 30: 983-997. [CrossRef]
https://doi.org/10.1080/10503307.2019.1699972
51. Oishi S, Takizawa T, Kamata N, Miyaji S, Tanaka K, Miyaoka H. Web-based training program using cognitive behavioral therapy to enhance cognitive flexibility and alleviate psychological distress among schoolteachers: pilot randomized controlled trial. JMIR Research Protocols 2018; 7. [CrossRef]
https://doi.org/10.2196/resprot.8541
52. Greenberg J, Reiner K, Meiran N. "Mind the trap": mindfulness practice reduces cognitive rigidity. PloS one 2012; 7. [CrossRef]
https://doi.org/10.1371/journal.pone.0036206
53. Johnco C, Wuthrich VM, Rapee RM. The influence of cognitive flexibility on treatment outcome and cognitive restructuring skill acquisition during cognitive behavioural treatment for anxiety and depression in older adults: Results of a pilot study. Behaviour Research and Therapy 2014; 57: 55-64. [CrossRef]
https://doi.org/10.1016/j.brat.2014.04.005
54. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. Perspectives on Psychological Science 2008; 3:400-424. [CrossRef]
https://doi.org/10.1111/j.1745-6924.2008.00088.x
55. Wilkinson PO, Croudace TJ, Goodyer IM. Rumination, anxiety, depressive symptoms and subsequent depression in adolescents at risk for psycho-pathology: a longitudinal cohort study. BMC Psychiatry 2013; 13: 1-9. [CrossRef]
https://doi.org/10.1186/1471-244X-13-250
56. Davis RN, Nolen-hoeksema S. Cognitive ınflexibility among ruminators and nonruminators. Cognitive Therapy and Research 2000, 24; 699-711. [CrossRef]
https://doi.org/10.1023/A:1005591412406

Evaluation of Cataract Surgery Outcomes in Geriatric Population with Geriatric Depression Scale

Gonca Ayşe Ünal[1], Ayşegül Barak Özer[2], Emin Serbülent Güçlü[3], Ömer Özer[4], Zeki Baysal[4]

1 Psychiatry Clinic, Mersin State Hospital, Mersin, Türkiye
2 Psychiatry Clinic, Niğde Training and Research Hospital, Niğde, Türkiye
3 Ophthalmology Clinic, Mersin State Hospital, Mersin, Türkiye
4 Department of Ophthalmology, Niğde Ömer Halisdemir University, Niğde, Türkiye

Abstract

Aim: To show the changes in geriatric depression scale (GDS) scores in patients undergoing senile cataract surgery.

Methods: A total of 74 patients aged 60 years and older who presented to the Mersin City E&R hospital Ophthalmology Clinic between January 01, 2023, and May 01, 2023, with low vision and underwent phacoemulsification surgery for senile cataract were included in this study. Patients with antidepressant use and/or ongoing follow-up and treatment for depression in a psychiatric clinic were excluded from this study. All patients were evaluated with the GDS before the surgery and the third month after surgery.

Results: When the distribution according to GDS is analyzed, 38 patients scored 0-10 points, 18 patients scored 11-13 points, 18 patients scored 14 points and above in the preoperative period. In the postoperative period, 49 patients scored 0-10 points, 14 patients scored 11-13 points, 11 patients scored 14 points and above. The mean preoperative GDS score was 10.22 ± 5.01, while the mean postoperative GDS score was 8.2 ± 4.92. There was a positive correlation (r=0.680 preoperative and r=0.801 postoperative) between visual acuity and GDS score in the preoperative period (p<0.001 for both).

Conclusions: Cataract surgery may potentially reduce the risk of depression or shorten the duration of depression in geriatric patients

Keywords: *Cataract, Depression, Elderly, Geriatric, Surgery*

1. Introduction

Senile cataract is an age-related ophthalmologic disease in which the lens becomes cloudy and causes visual loss[1]. It is one of the most common causes of visual impairment worldwide[1,2]. In 2020, cataract caused approximately 15.2 million cases of blindness and 78.8 million cases of visual impairment in the population over 50 years of age[3]. Depending on the severity of the disease, patients complain of blurred vision, distance and/or near low vision. Such ocular symptoms can cause great discomfort and stress. A study in 2022 reported that adults with self-reported general visual impairment had higher Kessler psychological distress scores[4]. Furthermore, cataract-related visual impairment can lead to limitations in mobility and activities of daily living, which can negatively affect mental health in older adults[5]. Therefore, the relationship between senile cataract and mental health is an important topic worthy of further research.

Major depressive disorder (MDD) is one of the most common mental disorders. To date, many studies have identified risk factors for MDD. Depression is more common in populations with chronic illnesses. The elderly in particular are more likely to suffer from chronic medical conditions, making them more prone to depression. Ocular diseases in the elderly have not yet been identified as a risk factor for MDD[6,7].

Many studies have reported on the relationship between cataract and depression. In 2020, a nationwide population-based longitudinal study in Taiwan revealed a significant association between cataract and increased risk of developing depression[8]. In a 2021 Span-

* Corresponding Author: Ömer Özer
e-mail: omerozer92@gmail.com
Received: 25.10.2023, Accepted: 26.02.2024, Available Online Date: 01.03.2024
Cite this article as: Ünal GA, Özer AB, Güçlü ES, et al. Evaluation of Cataract Surgery Outcomes in Geriatric Population with Geriatric Depression Scale. J Cukurova Anesth Surg. 2024; 7(1)): 8-11. https://doi.org/10.36516/ jocass.1395860

ish cross-sectional analysis focusing on cataract patients with diabetes, only women were significantly associated with higher rates of depression[9].

The relationship between cataract and depression needs to be further investigated, as previous studies have not yielded conclusive results. The aim of this study was to show the changes in geriatric depression scale scores in patients undergoing senile cataract surgery.

2. Materials and methods

A total of 74 patients aged 60 years and older who presented to the Mersin City Hospital Ophthalmology Clinic between January 01, 2023 and May 01, 2023 with low vision and underwent phacoemulsification surgery for senile cataract were included in this study. Patients with antidepressant use and/or ongoing follow-up and treatment for depression in a psychiatric clinic were excluded from this study. Written informed consent was obtained from all participants. The necessary permissions were obtained from Toros University Scientific Research and Publication Ethics Committee (2023/122-27/10/2023). The study was conducted in accordance with the Declaration of Helsinki.

Geriatric depression score is a scale that can be used for the diagnosis of depression in the geriatric population and its Turkish validity and reliability study was conducted by Ertan and Eren. In this scoring, 0 to 10 points are classified as "no depression", 11 to 13 points as "probable depression" and 14 points or more as "definite depression" [10].

Patients were divided into three groups according to preoperative visual acuity level. Patients in group 1 had best corrected visual acuity (BCVA) logMAR 0.3 to 0.6, patients in group 2 had BCVA logMAR 0.7 to 1.0 and patients in group 3 had BCVA logMAR 1.1 to 2.0. Cataract surgery was not performed in patients with BCVA logMAR 0.3 and above. Age and gender of all patients were recorded. A geriatric depression scale was administered to all patients by a specialized psychiatrist before cataract surgery. The GDS was administered again by the same psychiatrist at the third month visit after uncomplicated cataract surgery and the results were compared.

Statistical analysis of the study data was performed with SPSS 24.0.1 package program (IBM Corp, Armonk, NY, USA). Categorical variables were expressed as number (n) and percentage (%) and continuous variables were expressed as mean ± standard deviation. The normal distribution of continuous variables was checked by Shapiro-Wilk test. Student's t test, paired t test and one-way ANOVA test were used to compare the means of the groups. The association between categorical variables was investigated by Chi-Square analysis. Statistical significance level was taken as $p<0.05$ for all comparisons.

Table 1

Age and gender distribution of the patients

	Overall		Group 1		Group 2		Group 3		p
N (%)	74 (100)		19 (25.7)		21 (28.4)		34 (45.9)		
Age (years)	72.16 ± 6.78		71.74 ± 7.35		73.19 ± 7.35		71.76 ± 6.21		0.719
Male (n, %)	38	51.4	9	47.4	11	52.4	18	52.9	0.921
Female (n, %)	36	48.6	10	52.6	10	47.6	16	47.1	

3. Results

The mean age of the patients was 72.16 ± 6.78 years. Of all patients, 38 (51.4%) were male. There were 19 patients in group 1 (preoperative BCVA logMAR between 0.3 and 0.6), 21 patients in group 2 (preoperative BCVA logMAR between 0.7 and 1.0) and 34 patients in group 3 (preoperative BCVA logMAR between 1.1 and 2.0). There was no difference in age and gender distribution between the groups (p=0.719 and p=0.921, respectively) (Table 1).

The mean preoperative BCVA was logMAR 1.06 ± 0.45 and the mean postoperative BCVA was logMAR 0.26 ± 0.14. The mean GDS in the preoperative period was 10.22 ± 5.01 and the mean GDS in the postoperative period was 8.2 ± 4.92. In all groups, the mean BCVA and GDS in the preoperative and postoperative periods were statistically significantly different (p<0.001, both) (Table 2).

When the distribution according to GDS is analysed, 38 patients scored 0-10 points, 18 patients scored 11-13 points, 18 patients scored 14 points and above in the preoperative period. In the postoperative period, 49 patients scored 0-10 points, 14 patients scored 11-13 points, 11 patients scored 14 points and above. There was no difference between preoperative and postoperative GDS scores in all patients (p=0.167). In Group 2, 8 patients scored 0-10 points, 6 patients scored 11-13 points, 7 patients scored 14 points or more in the preoperative period. In the postoperative period, 16 patients scored 0-10 points, 4 patients scored 11-13 points, and 1 patient scored 14 points or more. In group 2, a statistically significant difference was observed between preoperative and postoperative GDS scores (p=0.023). (Table 3)

There was a positive correlation between BCVA in the preoperative period and GDS score (r=0.680 for preoperative and r=0.801 for postoperative) (p<0.001, both). There was a positive correlation (r=0.443) between BCVA in the postoperative period and postoperative GDS scores (p<0.001) (Table 4).

Table 2

Visual acuity and geriatric depression scale results before and after surgery

	Overall	Group 1	Group 2	Group 3
N (%)	74 (100)	19 (25.7)	21 (28.4)	34 (45.9)
VA pre-op	1.06 ± 0.45	0.5 ± 0.11	0.9 ± 0.11	1.47 ± 0.26
VA post-op	0.26 ± 0.14	0.12 ± 0.07	0.26 ± 0.10	0.35 ± 0.12
p	<0.001			
GDS pre-op	10.22 ± 5.01	6.05 ± 3.27	11.14 ± 4.99	11.97 ± 4.58
GDS post-op	8.2 ± 4.92	4.58 ± 3.01	6.62 ± 4.15	11.21 ± 4.43
p	<0.001			

VA: Visual acuity, GDS: Geriatric depression scale

4. Discussion

The relationship between cataract and depression is an increasingly important research topic. These conditions, which affect older people in society and are quite common, can also be seen together. At the same time, senile cataracts cause negative effects on people's comfort due to the loss of vision it causes.

In study, a community-based sample of 662 people aged over 70 years was selected.

Table 3

Distribution of patients according to GDS scores before and after surgery

	Overall		Group 1		Group 2		Group 3		p1	p2
N (%)	74 (100)		19 (25.7)		21 (28.4)		34 (45.9)			
GDS	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop		
0 - 10 points	38	49	18	19	8	16	12	14		
11 - 13 points	18	14	1	0	6	4	11	10	<0.001	<0.001
14 - 30 points	18	11	0	0	7	1	11	10		
p3	0.167		0.311		0.023		0.883			

GDS: Geriatric depression scale, p1: Intergroup comparison before surgery, p2: Intergroup comparison after surgery, p3: Intragroup comparison before and after surgery

Table 4

Correlation analysis of the study parameters

		VA pre-op	VA post-op	GDS pre-op	GDS post-op
Age (years)	r	-0.089	0.074	-0.088	-0.110
	p	0.453	0.534	0.455	0.351
VA pre-op	r		0.656	0.680	0.801
	p		<0.001	<0.001	<0.001
VA post-op	r			0.393	0.443
	p			<0.001	<0.001
GDS pre-op	r				0.919
	p				<0.001

VA: Visual acuity, GDS: Geriatric depression scale

The number of patients with clinically significant depressive symptoms was calculated to be 6.7% in cataract patients[11]. In a meta-analysis of different disease categories, the prevalence of depression was highest for dry eye disease at 29%, followed by glaucoma, age-related macular degeneration and cataract patients at 23%[12]. An Australian study included 329 participants with cataract. The prevalence of depressive symptoms among patients was 28.6%[13]. A total of 813 adults awaiting cataract surgery participated in a multicenter prospective cohort study, of which 456 (56.1%) were male. The prevalence of high depression score was reported as 87.4%[14].

A Chinese study evaluated depression among cataract patients. It was found that high anxiety scores and low visual acuity in the better seeing eye were risk factors for depression in cataract patients. In the same study, both anxiety and depression scores decreased after surgery[15].

A meta-analysis on this subject included 16 studies. Depression in cataract patients decreased significantly after surgery (p<0.001). In addition, in 6 controlled studies, the decrease in depression was higher in the surgical patient group than in the control group (p=0.019)[16].

A population-based study investigated the effect of cataract on depression risk and the benefits of cataract surgery. A total of 233,258 patients were included. At a mean follow-up of 7.8 years, cataract was significantly associated with an increased risk of developing depression (hazard ratio [HR]=1.78, p<0.001). In particular, a lower risk of depression was reported in patients who underwent surgery for cataract compared to those who did not (HR=0.75, p<0.001)[8].

In a study conducted by Meuleners et al., mental health outpatient clinic visits for depression and/or anxiety were evaluated in patients who underwent cataract surgery. It was shown that one year after cataract surgery, there was a significant decrease of 18.8% (p ≤ 0.001) in the number of mental health visits for depression and/or anxiety. The corresponding reduction in healthcare expenditure for the treatment of depression and/or anxiety was 28%[17].

In a study conducted in Montreal, 672 patients were examined. While 41% of patients had an BCVA of 6/18 or worse, 26% had symptoms of depression before surgery. In the logistic regression model, those with BCVA ≤6/18 had a 59% higher probability of depression[18].

In one study in the literature, 100 patients were evaluated. It was shown that the most depressed patients were those suffering from age-related macular degeneration and proliferative diabetic retinopathy, as well as glaucoma and cataracts[19].

In an observational prospective study of a cohort of 150 patients undergoing cataract surgery and assessed for changes in depressive symptomatology, the difference in pre- and postoperative depression scores correlated with the difference in pre- and postoperative BCVA (p<0.001). Paired sample t-test revealed a statistically significant difference between pre- and postoperative depression scores (p<0.001). Paired sample Wilcoxon signed-rank test revealed a statistically significant improvement in depression status (p=0.004)[20].

A community-based study evaluated 4611 Chinese adults aged 60 years and older. Adults with cataract were found to be more likely to have depressive symptoms than those without[21].

In a study involving 413 participants scheduled for cataract surgery, there was a significant decrease (improvement) of one point in the depressive symptoms score after cataract surgery (p=0.04)[22].

In another study, participants were evaluated with the Geriatric Depression Scale (GDS) one day before and three months after cataract surgery. The mean postoperative visual acuity improvement was 0.77±0.18 and the mean GDS score difference was -1.49±1.72. Postoperative improvement in visual acuity and GDS scores were statistically significant (p=0.001)[23].

In our study, the prevalence of depression among cataract patients was found to be 24.3% (18/74). This rate decreased to 14.9% after cataract surgery (11/74). At the same time, both preoperative and postoperative VA levels and GDS scores had a statistically significant correlation. In our study, the patients who benefited most from cataract surgery in terms of depression were those with a preoperative visual acuity between logMAR 0.7 and 1.0 (group 2). Patients with a preoperative visual acuity of 1.1 or above were considered to have other comorbidities (glaucoma and/or age-related macular degeneration) that were probably the cause of visual loss. Therefore, cataract surgery may not have fully reflected the expected positive effect. Large-scale studies are needed to evaluate the effect clearly.

In conclusion, screening for depression in senile cataract patients is important and cataract surgery has been reported to have a beneficial effect in reducing the risk of depression. It should be taken into consideration that older adults who have limitations in daily tasks due to visual impairment may be more functional after cataract surgery. Cataract surgery in these patients may potentially reduce the risk of depression or shorten the duration of depression.

Statement of ethics

The study was approved by the Toros University Scientific Research and Publication Ethics Committee (2023/122-27/10/2023).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1.Abraham AG, Condon NG, West Gower E. The new epidemiology of cataract. Ophthalmol Clin North Am. 2006 Dec;19(4):415-25. https://doi.org/10.1016/j.ohc.2006.07.008
2.Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004 Nov;82(11):844-51.
3.GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021 Feb;9(2):e144-e160. https://doi.org/10.1016/S2214-109X(20)30489-7
4.Lundeen EA, Saydah S, Ehrlich JR, et al. Self-Reported Vision Impairment and Psychological Distress in U.S. Adults. Ophthalmic Epidemiol. 2022 Apr;29(2):171-81. https://doi.org/10.1080/09286586.2021.1918177
5.Lampinen P, Heikkinen E. Reduced mobility and physical activity as predictors of depressive symptoms among community-dwelling older adults: an eight-year follow-up study. Aging Clin Exp Res. 2003 Jun;15(3):205-11. https://doi.org/10.1007/BF03324501
6.Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry. 2010;22(5):429-36. https://doi.org/10.3109/09540261.2010.492391
7.Schoevers RA, Smit F, Deeg DJ, et al. Prevention of late-life depression in primary care: do we know where to begin? Am J Psychiatry. 2006 Sep;163(9):1611-21. https://doi.org/10.1176/ajp.2006.163.9.1611
8.Chen PW, Liu PP, Lin SM, et al. Cataract and the increased risk of depression in general population: a 16-year nationwide population-based longitudinal study. Sci Rep. 2020 Aug 7;10(1):13421. https://doi.org/10.1038/s41598-020-70285-7
9.López Sánchez GF, Smith L, Jacob L, et al. Gender Differences in the Association Between Cataract and Mental Health in Adults With Diabetes: A Cross-Sectional Analysis From the Spanish National Health Survey 2017. Front Public Health. 2021 Dec 7;9:769155. https://doi.org/10.3389/fpubh.2021.769155
10.Ertan T, Eker E. Reliability, validity, and factor structure of the geriatric depression scale in Turkish elderly: are there different factor structures for different cultures? Int Psychogeriatr. 2000 Jun;12(2):163-72. https://doi.org/10.1017/s1041610200006293
11.Eramudugolla R, Wood J, Anstey KJ. Co-morbidity of depression and anxiety in common age-related eye diseases: a population-based study of 662 adults. Front Aging Neurosci. 2013 Oct 2;5:56. https://doi.org/10.3389/fnagi.2013.00056
12.Zheng Y, Wu X, Lin X, et al. The Prevalence of Depression and Depressive Symptoms among Eye Disease Patients: A Systematic Review and Meta-analysis. Sci Rep. 2017 Apr 12;7:46453. https://doi.org/10.1038/srep46453
13.Palagyi A, Rogers K, Meuleners L, et al. Depressive symptoms in older adults awaiting cataract surgery. Clin Exp Ophthalmol. 2016 Dec;44(9):789-96. https://doi.org/10.1111/ceo.12800
14.Kumar SGP, Ranpise D, Chavan S, et al. Depressive and generalized anxiety symptoms in adults awaiting cataract surgery in India. Natl Med J India. 2022 Nov-Dec;35(6):348-56. https://doi.org/10.25259/NMJI_35_6_348
15.Zhang D, Fan Z, Gao X, et al. Illness uncertainty, anxiety and depression in Chinese patients with glaucoma or cataract. Sci Rep. 2018 Aug 3;8(1):11671. https://doi.org/10.1038/s41598-018-29489-1
16.Pellegrini M, Bernabei F, Schiavi C, et al. Impact of cataract surgery on depression and cognitive function: Systematic review and meta-analysis. Clin Exp Ophthalmol. 2020 Jul;48(5):593-601. https://doi.org/10.1111/ceo.13754.
17.Meuleners LB, Hendrie D, Fraser ML, et al. The impact of first eye cataract surgery on mental health contacts for depression and/or anxiety: a population-based study using linked data. Acta Ophthalmol. 2013 Sep;91(6):e445-9. https://doi.org/10.1111/aos.12124
18.Freeman EE, Gresset J, Djafari F, et al. Cataract-related vision loss and depression in a cohort of patients awaiting cataract surgery. Can J Ophthalmol. 2009 Apr;44(2):171-6. https://doi.org/10.3129/i09-001.
19.Pop-Jordanova N, Ristova J, Loleska S. Depression in ophthalmological patients. Pril (Makedon Akad Nauk Umet Odd Med Nauki). 2014;35(2):53-8. https://doi.org/10.2478/prilozi-2014-0007
20.Mylona I, Aletras V, Ziakas N, et al. Successful Cataract Surgery Leads to an Improvement in Depressive Symptomatology. Ophthalmic Res. 2021;64(1):50-4. https://doi.org/10.1159/000508954
21.Wang H, Sun HP, Wang P, et al. Cataract and Depressive Symptoms among Older Chinese Adults. Optom Vis Sci. 2016 Dec;93(12):1479-84. https://doi.org/10.1097/OPX.0000000000000960
22. To KG, Meuleners LB, Fraser ML, et al. The impact of cataract surgery on depressive symptoms for bilateral cataract patients in Ho Chi Minh City, Vietnam. Int Psychogeriatr. 2014 Feb;26(2):307-13. https://doi.org/10.1017/S1041610213001907
23.Kheirkhah F, Roustaei G, Mohebbi Abivardi E, et al. Improvement in Cognitive Status and Depressive Symptoms Three Months after Cataract Surgery. Caspian J Intern Med. 2018 Fall;9(4):386-92. https://doi.org/10.22088/cjim.9.4.386

Predictive Value of HALP Score in The Early Stage of NSTEMI

Goknur Yıldız[1], Fatih Alper Ayyıldız[1], Özge Turgay Yıldırım[2]

1 Emergency Department of Eskisehir City Hospital, Eskisehir, Türkiye
2 Cardiology Department of Eskisehir City Hospital, Eskisehir, Türkiye

Abstract

Aim: Several inflammatory markers are associated with coronary artery disease severity and worse cardiovascular outcomes. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score are an indicator of inflammation and nutritional status. We aimed to evaluate the practicality of HALP score in non-ST elevation myocardial infarction (NSTEMI) patients.

Methods: This study was designed as a retrospective cohort study. Patients over the age of 18 who have been diagnosed with acute coronary syndrome were retrospectively searched from hospital records. The study groups were formed according to the results of the coronary angiography. Demographic data such as age, gender, total blood count, albumin levels, troponin levels and HALP scores of the patients were analyzed and comparisons between the groups were made decisively.

Results: 201 patients were enrolled in the study and the data was obtained from hospital records retrospectively. 79 patients were excluded from the study due to ST segment elevation myocardial infarction (STEMI). The study population was collected under two groups; the NSTEMI group (n=66) and normal coronary arteries (NCA) group (n=56). The mean age of NSTEMI group was 62.3 ± 11.8 and 71.2% (n=47) was male. The mean age of NCA group was 51.8 ± 9.2 and 30.3% (n=17) was male. There were statistically significant difference between NSTEMI and NCA groups in term of age and gender ($p<0.05$). The HALP score was statistically higher in NSTEMI group compared to NCA group ($p<0.001$). Age and HALP score have explanatory powers on NSTEMI patients ($p=0.001$ and $p=0.022$, in order of).

Conclusions: HALP score may be used as an easily applicable and inexpensive method in clinical practice that can contribute to the early diagnosis of NSTEMI patients.

Keywords: *NSTEMI, emergency department, HALP score*

1. Introduction

Heart disease is among the first causes of death in the world and it causes major health problems and economic difficulties[1]. Acute coronary syndrome (ACS) takes the first place in heart diseases and defines the general of ischemic myocardial disease and includes diagnoses covering ST segment elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). There are many events that can cause ACS, but the most common condition in its pathogenesis is plaque rupture and the resulting coronary artery thrombosis.

* Corresponding Author: Goknur Yıldız, e-mail: goknur_yldz@hotmail.com
Received: 26.10.2023, Accepted: 18.01.2024, Available Online Date: 01.03.2024
Cite this article as: Yıldız G, Ayyıldız FA, Turgay Yıldırım O. Predictive Value of HALP Score in The Early Stage of NSTEMI. J Cukurova Anesth Surg. 2024; 7(1)): 12-6. https://doi.org/10.36516/jocass.1396148

NSTEMI is caused by an imbalance in the oxygen supply and demand of the myocardium, which is formed as a result of partial obstruction of the coronary arteries and in this case, subendocardial ischemia and necrosis are observed[2]. This can damage the heart and disrupt its ability to pump blood throughout the body.

NSTEMI can be life threatening and cause lasting damage to the organs and increase the risk of subsequent heart problems. Clinical studies in NSTEMI show that outcomes improve with early invasive intervention. Therefore, early recognition of high-risk patients is of great importance. To date, many biomarkers and risk scores have been used for this reason[3]. The existence of cheap and easily accessible biomarkers is useful and life-saving in the diagnosis and follow-up of patients in NSTEMI, as in many diseases.

According to the conducted studies, inflammation has an important place in the development of atherosclerosis and cardiovascular diseases[4]. Inflammation and oxidative stress can cause plaque rupture, which in turn causes cardiovascular conditions[4]. Inflammatory markers affect the clinical course of coronary artery disease

(CAD) and associated with the occurrence of worse cardiovascular events[5]. Recent studies have also shown that many acute phase proteins (APPs) such as C- reactive protein, albumin are associated with the development of CAD, the severity of CAD, stroke, the presence of peripheral arterial disease and adverse cardiovascular conditions[6]. Anemia, hypoalbuminemia, hypoproteinemia and some mineral deficiencies such as iron and zinc are markers indicating malnutrition. Anemia is also causes cardiac decompensation and increases mortality rates[7]. Lymphocytes have an important role in inflammation. Since high platelet levels cause thromboembolism and atherosclerotic conditions, it has been found that it increases mortality[8]. Besides, white blood cell count to mean platelet volume ratio (WMR), is a marker of inflammation in atherosclerotic diseases and STEMI patients[9].

The HALP score (Hemoglobin, albumin, lymphocyte and platelet score) is an easy-to-measure parameter indicating nutritional condition and systemic inflammation[10] and has been suggested that it is an important prognostic marker in many cancer patients[11], acute heart failure[12], stroke[13] and acute ST elevation myocardial infarction[14]. However, it is unknown whether the HALP score has diagnostic value in terms of early diagnosis and therapy in NSTEMI patients. Therefore, in our study, we aimed to evaluate the predictive worth of the HALP score in patients with NSTEMI.

2. Materials and methods

This study was conducted in the emergency department of a tertiary hospital. Patients over the age of 18 who have been diagnosed with ACS in the emergency department and admitted to the coronary intensive care unit for the purpose of performing coronary angiography within a six-month period were recorded. Demographic data such as age, gender, and ECGs of the patients were analyzed during the emergency department admission.

Hemoglobin, neutrophil, lymphocyte, platelets, albumin and troponin results during the admission were recorded. An automated analyzing device was used for blood counts and analysis of biochemical markers (Cell_Dyn Ruby Hematology Analyzer, Architect c8000 Clinical Chemistry). The HALP score was measured with the hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) / platelet count (/L) process10,11.

Patients were grouped into STEMI, NSTEMI and UAP groups according to their ECG and troponin levels at the time of admission. Patients with ST elevation on their ECG and diagnosed with STEMI at the time of admission were excluded from the study. After excluding STEMI patients, the study population was divided into NSTEMI and normal coronary artery (NCA) groups. Patients who did not have ST elevation on ECG and were found to have elevated troponin at the time of admission were included in the NSTEMI group. Patients hospitalized with the diagnosis of UAP were also evaluated according to the results of coronary angiography. Patients hospitalized with the diagnosis of UAP and found to have coronary artery occlusion in their angiography were included in the NSTEMI group. On the other hand, patients hospitalized with the diagnosis of UAP and no coronary artery occlusion detected in angiography were included in the NCA group.

Patients under 18 years of age were excluded from the study.

2.1. Statistical Analysis

Data which for continuous variables with normal distribution are indicated as mean ± standard deviation, for variables which are not normally distributed and as numbers and proportions for categorical variables are indicated as median (interquartile range). The Shapiro-Wilk test was used to determine whether the data showed a normal distribution, and the Levene test was used to assess whether the group variances were homogeneous. Binary logistic regression analysis is used to define the predictive value of risk factors with the ACS. ROC (Receiver operating characteristic) curve was applied to examine the cut-off value, sensitivity and specificity of the HALP score on NSTEMI diagnosis. Analyses of the data are performed using SPSS 20.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA). A p-value of <0.05 is determined statistically significant.

While conducting this study, the Helsinki Declaration was complied with and accepted by the local ethics committee (ESH/GOEK 2022/3).

3. Results

During the 6-month study period, 201 patients who were admitted to the Cardiology Intensive Care Unit for angiography after being diagnosed with ACS were enrolled in the study. 79 patients were excluded from the study due to STEMI. According to the results of angiography, coronary artery occlusion was detected in 66 patients and they were enrolled in the study (NSTEMI) group with the diagnosis of NSTEMI. The remaining 56 patients had normal coronary arteries as a result of angiography and were enrolled in the NCA group (Figure 1).

The mean age of NSTEMI group was 62.3 ± 11.8 and 71.2% (n=47) was male. The mean age of NCA group was 51.8 ± 9.2 and 30.3% (n=17) was male. There were statistically significant difference between NSTEMI and NCA groups in term of age and gender (p<0.05).

No significant difference was seen at hemoglobin, albumin and lymphocyte counts (p>0.05). The troponin levels were higher in NSTEMI group (p<0.001) and platelet count was higher in NCA group (p=0.001).

Figure 1

Flow-chart of the patient selection

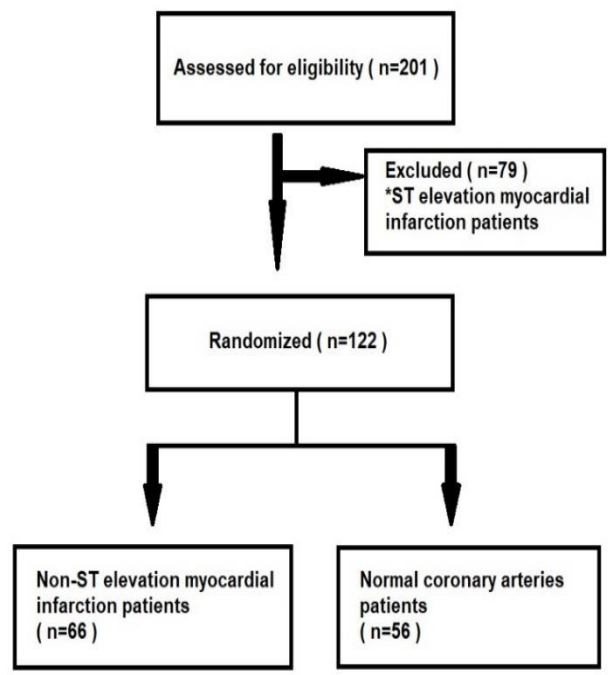


Table 1

Characteristics of the patient groups

	NSTEMI (n=66)	Normal coronary arteries (n=56)	P
Age, year	62.3 ± 11.8	51.8 ± 9.2	<0.001
Gender, male, n (%)	47 (71.2%)	17 (30.3%)	<0.001
Hemoglobin, g/dl	14.2 ± 2.1	13.4 ± 1.8	0.014
Albumin, g/dl	43.6 (40.0 – 45.7)	42.7 (41.0 – 45.4)	0.875
Lymphocyte (*10^3)	2.5 (1.9 – 3.2)	2.8 (1.9 – 2.8)	0.080
Platelet (*10^3)	227.3 ± 57.0	266.3 ± 71.0	0.001
Troponin, ng/l	249.4 (45.5 – 1015.9)	13.6 (1.1 – 39.5)	<0.001
HALP score	7.3 (5.1 – 10.0)	5.1 (3.9 – 6.4)	<0.001

The HALP score was statistically higher in NSTEMI group compared to NCA group (7.3 (5.1 – 10.0) for NSTEMI group and 5.1 (3.9 – 6.4) for NCA group, p<0.001). The main characteristics of the patient groups are shown in Table 1.

The binary logistic regression analysis was used to evaluate the impact of risk factors and laboratory parameters on NSTEMI patients. Age and HALP score have explanatory powers on NSTEMI patients (p=0.001 and p=0.022, in order of) (Table 2).

ROC curve analysis was formed to predict the best cut off value for HALP to predict NSTEMI in patients. The area under the curve was 0.706 which is an acceptable value. Best cut of value was 5.58 with 69.7% sensitivity and 62.5% specificity (Figure 2).

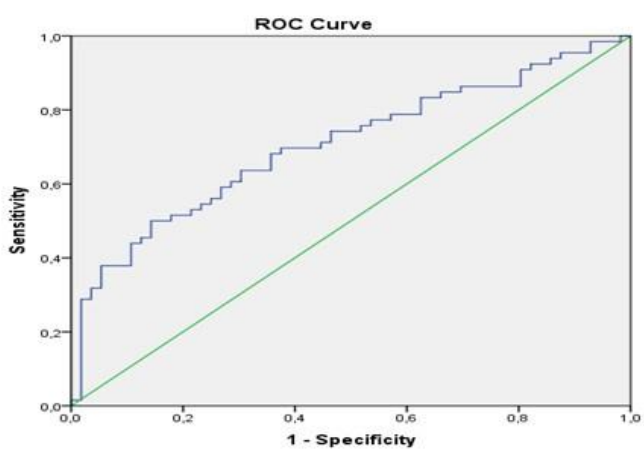
Table 2

Visual acuity and geriatric depression scale results before and after surgery

Variable	Odds Ratio	95% Confidence Interval	P
Age	1.225	1.084-1.384	0.001
Gender	0.131	0.017-1.025	0.053
Troponin	1.002	1.000-1.004	0.054
HALP score	1.854	1.093-3.143	0.022
Constant	0.000		0.002

Figure 2

ROC Curve for HALP Score



4. Discussion

NSTEMI is a life-threatening condition that can cause multiple organ damage if not treated early. For this reason, it needs many early diagnostic and predictive tests. In our study, the diagnostic value of the recently determined HALP score was investigated in NSTEMI patients.

The HALP score was initially described to evaluate survival in gastric cancer[15]. After it has been used to evaluate survival in many cancer types and in patients with ischemic stroke[11,13]. The HALP score is a newly established, valuable marker that provides information about the patient's nutritional status and systemic inflammation. With this marker, the general health status of the patient is evaluated according to hemoglobin, albumin, lymphocyte and platelet values. In recent studies it has been shown that lower HALP score is associated with shorter survival[10,13]. In the study of Cay et al. in patients who had undergone bariatric surgery, it has been found that those with a high HALP score lose weight more easily and the improvement in laboratory values is more significant[16]. With this study, we evaluated the HALP score in NSTEMI patients and this is a first in the literature.

The first of the markers evaluated in the HALP score is hemoglobin value. Anemia is an indicator of poor prognosis in patients with CAD, including NSTEMI[17]. Similar results were found in many studies in the literature. But, we did not find a statistically significant difference in terms of hemoglobin level between NSTEMI group and NCA group in this study.

The second parameter of the score is albumin, which is present in the intravascular space as the main protein. Albumin has an important role in many physiological functions. In addition, a decrease in serum albumin may lead to an increase in poor clinical outcomes in coronary artery disease (CAD)[18]. In our study, we found the serum albumin result of patients with NSTEMI to be higher than the level of NCA, but there was no statistically significant difference.

Lymphopenia is a parameter that can be an indicator of a poor prognosis in CAD patients[19]. In our study, we found the lymphocyte level, which is the third marker of HALP score, higher in patients with NCA compared to NSTEMI patients, but no statistically significant difference was found.

Platelets have a very important place in the formation of ACS. Both high and low platelet counts can be seen in CAD. Some studies have found that increases in platelet levels lead to thromboembolism and atherosclerotic conditions, and these conditions cause an increase in deaths due to CAD[20,21]. However, studies conducted on intensive care patients have shown that a low platelet count worsens the prognosis of patients and increases mortality[22]. Also low platelet levels are also used to predict poor clinical results in patients with ACS[23]. In our study, the platelet level, which is the fourth marker, was detected lower in NSTEMI patients and there was statistically significant difference.

Studies have established that the HALP score can indicate the nutritional-inflammation condition of patients[10,24] and has been proven that it is an important prognostic marker for patients with cancer[25]. There are limited studies in which the HALP score has been evaluated in non-cancer cases. In a study conducted by Kocaoğlu et al.[26], in intensive care patients, the utility of HALP score to estimate mortality was examined and the HALP score was not found to be good predictor of prognosis in intensive care patients. In another study conducted by Kocaoglu et al.[12], HALP score and modified HALP (m-HALP) score were evaluated in patients with acute heart failure and it was found that the m-HALP score is more important predictor in determining the 3-month mortality in patients with acute heart failure. On the other hand, it was found that the classical HALP score was not statistically significant. In a study

conducted by Tian et al.[13], in acute ischemic stroke (AIS) patients, the relationship between HALP score and poor clinical conditions was examined and found that HALP score can be an important indicator of death and recurrent stroke in patients with AIS. In a study conducted by Karakayalı et al.[14], in STEMI patients undergoing primary percutaneous coronary intervention, the HALP score was found to be a significant independent predictor of in-hospital mortality. In our study, HALP score at admission was found higher in NSTEMI patients and there was statistically significant difference.

Limitations

The major limitation of our study is the small sample size. Also, the retrospective design of the study caused us not to be able to access the data of some patients.

5. Conclusion

Our study proved that, the HALP score is an easily applicable and inexpensive method in clinical practice that can contribute to the early diagnosis of NSTEMI patients. Although these findings are not sufficient to apply in a clinical approach according to current guideline recommendations, future studies on similar subjects and increased data may change future practices.

Statement of ethics

The study was approved by the local ethics committee (ESH/GOEK 2022/3).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Contribution Details

Göknur Yıldız: Design, Literature search, Data acquisition, Manuscript preparation, Manuscript editing, Manuscript review, Guarantor

Fatih Alper Ayyıldız: Design, Data acquisition, Manuscript preparation, Manuscript editing, Guarantor

Özge Turgay Yıldırım: Design, Data analysis, Statistical analysis, Manuscript editing

References

1.Blais C, Rochette L, Ouellet S, et al. Complex evolution of epidemiology of vascular diseases, including increased disease burden: from 2000 to 2015. Can J Cardiol. 2020;36(5):740-6.
https://doi.org/10.1016/j.cjca.2019.10.021
2.Reigle J. Coronary circulation disorders. In: Sorenson M, Quinn L, Klein D, editors. Pathophysiology: concepts of human disease. Hoboken (NJ): Pearson; 2019. p. 572–611.
3.D'Ascenzo F, Biondi-Zoccai G, Moretti C, et al. TIMI, GRACE and alternative risk scores in acute coronary syndromes: a metaanalysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials. 2012;33:507-14.
https://doi.org/10.1016/j.cct.2012.01.001
4.Zhang DP, Mao XF, Wu TT, et al. The fibrinogen-to-albumin ratio is associated with outcomes in patients with coronary artery disease who underwent percutaneous coronary intervention. Clin Appl Thromb Hemost. 2020;26:1076029620933008.
https://doi.org/10.1177/1076029620933008
5.Zhou D, Wang G, Fan Y, et al. Platelet to lymphocyte ratio is associated with the severity of coronary artery disease and clinical outcomes of percutaneous coronary intervention in the Chinese Han population. Exp Ther Med 2017;13:731–8.
https://doi.org/10.3892/etm.2016.3993
6.Cagdas M, Rencuzoğullari I, Karakoyun S, et al. Assessment of relationship between C-reactive protein to albumin ratio and coronary artery disease severity in patients with acute coronary syndrome. Angiology 2017;70:361–8.
https://doi.org/10.1177/0003319717743325
7.Teng TH, Finn J, Hung J. Mild anaemia is associated with increased all-cause mortality in heart failure. Heart Lung Circ 2010;19: 31–7.
https://doi.org/10.1016/j.hlc.2009.08.004
8.Reininger AJ, Bernlochner I, Penz SM, et al. A 2-step mechanism of arterial thrombus formation induced by human atherosclerotic plaques. J Am Coll Cardiol 2010;55(11): 1147-58.
https://doi.org/10.1016/j.jacc.2009.11.051
9.Karakayali M, Omar T, Artac I, et al. The White Blood Cell Count to Mean Platelet Volume Ratio (WMR) is Associated With Syntax Score in Patients With ST-Segment Elevation Myocardial Infarction. Kafkas J Med Sci 2023; 13(2):173–8.
https://doi.org/10.5505/kjms.2023.98512
10.Xu SS, Li S, Xu HX, et al. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. World J Gastroenterol. 2020;26:828–38.
https://doi.org/10.3748/wjg.v26.i8.828
11.Guo Y, Shi D, Zhang J, et al. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel significant prognostic factor for patients with metastatic prostate cancer undergoing cytoreductive radical prostatectomy. J Cancer. 2019;10:81– 91.
https://doi.org/10.7150/jca.27210
12.Kocaoğlu S, Alatlı T. The Efficiency of the HALP Score and the Modified HALP Score in Predicting Mortality in Patients with Acute Heart Failure Presenting to the Emergency Department. Journal of the College of Physicians and Surgeons Pakistan 2022, Vol. 32(06): 706-11.
13.Tian M, Li Y, Wang X, et al. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is associated with poor outcome of acute ischemic stroke. Front Neurol 2021;11:610318.
https://doi.org/10.3389/fneur. 2020.610318
14.Karakayalı M, Omar T, Artac I, et al. The prognostic value of HALP score in predicting in-hospital mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Coron Artery Dis. 2023:1;34(7):483-8.
https://doi.org/10.1097/MCA.0000000000001271
15.Chen XL, Xue L, Wang W, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: A retrospective cohort study. Oncotarget 2015;6(38):41370-382.
https://doi.org/10.18632/oncotarget.5629
16.Cay F, Duran A. Predictive factors of success in sleeve gastrectomy: One-year follow-up and the significance of HALP score. J Coll Physicians Surg Pak 2021;31(12):1406-11.
https://doi.org/10.29271/jcpsp.2021.12.1406
17.Pang WW, Schrier SL. Anemia in the elderly. Curr Opin Hematol 2012;19: 133–40.
18.Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8-12.
19.Ommen SR, Gibbons RJ, Hodge DO, et al. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997;79(6):812-4.
https://doi.org/10.1016/s0002-9149(96)00878-8
20.Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology. 2019;70(9):802-18.
21.Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. BMJ Open. 2019;9(1):e022896.
22.Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. Crit Care Med 2000;28(6):1871-6.
https://doi.org/10.1097/0000 3246-200006000-00031
23.Yadav M, Généreux P, Giustino G, et al. Efect of baseline thrombocytopenia on ischemic outcomes in patients with acute coronary syndromes who undergo percutaneous coronary intervention. Can J Cardiol 2016;32:226–33.
24.Peng D, Zhang CJ, Tang Q, et al. Prognostic significance of the combination of preoperative hemoglobin and albumin levels and lymphocyte and platelet

counts (HALP) in patients with renal cell carcinoma after nephrectomy. BMC Urol. 2018;18:20.
https://doi.org/10.1186/s12894-018-0333-8
25.Shen XB, Zhang YX, Wang W, et al. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with small cell lung cancer before first-line treatment with etoposide and progression-free survival. Med Sci Monit. 2019;25:5630–9.
https://doi.org/10.12659/MSM.917968
26.Kocaoğlu S, Alatlı T. The efficiency of HALP score, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in predicting mortality in intensive care patients. J Health Sci Med 2022;5(1): 201-6.

Evaluation of the Relationship Between Estimated Right Atrial Pressure and Fibrosis-4 Index in Patients with Congenital Heart Disease

Mert Evlice[1]

1 Cardiology Department of Adana City Hospital, Adana, Türkiye

Abstract

Aim: The fibrosis-4 index is a non-invasive and reproducible approach to assess liver stiffness (LS). LS has been reported to be associated with fibrosis but mean right atrial pressure can also influence LS values. We aimed to evaluate the relationship between fibrosis-4 index and echocardiographically estimated right atrial pressure in adults with congenital heart disease.

Methods: This study was conducted at a tertiary heart center between January 2021 and January 2023. A total of 127 patients with congenital heart disease were included in the study. The fibrosis 4 index was calculated. The fibrosis-4 index was calculated as follows: Fibrosis-4 index = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count (109/L)](14). Echocardiographic measurements were analyzed. The inferior vena diameter and collapsibility index were calculated and the estimated right atrial pressure was evaluated.

Results: Study patients included 75 women (59%) with a mean age of 50 ± 9.9 years. Fibrosis-4 index was significantly correlated with TRV max (r = 0.51, p < 0.001), estimated right atrial pressure (r = 0.63, p < 0.001), estimated systolic pulmonary artery pressure (r = 0.42, p < 0.001), IVC diameter (r = 0.62, p < 0.001), IVC collapsibility (r = 0.464, p < 0.001), and NT-proBNp value (r = 0.624, p < 0.001). The fibrosis-4 index was also significantly correlated with the degree of tricuspid valve insufficiency(r = 0.342, p < 0.001), RV basal diameter (r = 0.294, p = 0.001), ASD diameter(r = 0.27, p = 0.002), Qp/Qs (r = 0.271, p = 0.003). However; the fibrosis 4 index was not significantly correlated with high-sensitive troponin (r = 0.11, p = 0.43). The fibrosis-4 index greater than 1.23 was associated with increased estimated right atrial pressure (IVC diameter > 21mm and IVC collapsibility < 50%), with a sensitivity of 95 % and a specificity of 74 % (AUC= 0.88; p<0.001; 95% CI: 0.82-0.94).

Conclusions: The fibrosis-4 index, which is a marker of liver congestion/stiffness/fibrosis, may be an important indicator in the echocardiographic determination of estimated mean right atrial pressure and the possibility of pulmonary hypertension in patients with congenital heart disease.

Keywords: *Congenital heart disease, estimated mean right atrial pressure, fibrosis-4 index, liver stiffness*

1. Introduction

The spectrum of chronic liver damage attributed to passive hepatic congestion that occurs in the setting of any cardiopulmonary disease that causes increased central venous pressure (right atrial pressure), such as right-sided heart failure, is referred to as congestive hepatopathy[1]. Common causes include biventricular insufficiency due to cardiomyopathy, severe pulmonary hypertension, right ventricular myocardial infarction, constrictive pericarditis, cor pulmonale, mitral valve stenosis, and valvulopathies such as tricuspid valve regurgitation. Since the pressure from the right ventricle is transmitted directly to the hepatic veins and sinusoids, insufficiency of the tricuspid valve causes passive congestion. If left untreated, long-standing congestion can lead to cardiac fibrosis and eventually cardiac cirrhosis[1].

There are approximately 1 million adult patients with congenital heart disease (CHD) in the United States, and the number is increasing[2]. Hepatic complications are common and may occur secondary to persistent chronic passive venous congestion or decreased cardiac output resulting from the underlying cardiac disease or as a re-

* Corresponding Author: Mert Evlice, e-mail: mertevlice@hotmail.com
Received: 20.01.2024, Accepted: 26.02.2024, Available Online Date: 01.03.2024
Cite this article as: Evlice M. Evaluation Of the Relationship Between Estimated Right Atrial Pressure and Fibrosis-4 Index in Patients with Congenital Heart Disease. J Cukurova Anesth Surg. 2024; 7(1)): 17-22.
https://doi.org/10.36516/jocass.1422888

sult of palliative cardiac surgery; transfusion or drug-related hepatitis may also occur. The unique physiology of Fontan circulation is particularly prone to the development of hepatic complications and is, in part, related to the duration of the Fontan procedure. Liver biochemical test abnormalities may be related to cardiac failure, resulting from intrinsic liver disease, secondary to palliative interventions, or drug-related[2,3].

Liver dysfunction is one of the important non-cardiac complications of CHD. According to an analysis of the German National CHD Register, it was observed in 6% of deceased patients suffering from CHD[4]. In a study, it was shown that cirrhosis occurred 11-15 years after Fontan surgery in patients under the age of 25[5]. For this reason, it is recommended to monitor non-cardiac complications, especially liver dysfunction[3,6,7].

Elevated mean right atrial pressure (RAP) measured by right heart catheterization is an established risk factor for poor survival in the Registry to Evaluate Early and Long-term pulmonary arterial hypertension Disease Management (REVEAL Registry) as well as other cohorts[8,9]. Echocardiography estimates of right atrial pressure have been validated against right heart catheterization in the general population and have shown a modest correlation in patients with pulmonary arterial hypertension[8,10]. While several methods have been studied, assessment of the inferior vena cava (IVC) diameter and percent collapsibility with inspiration or "sniff" is the most widely used and accepted[8,10,11].

Non-invasive liver stiffness value of liver ultrasonography determines the average mean RAP independently in patients with and without heart failure. LS measurement was thought to be a cheap, simple, and non-invasive follow-up parameter that could be used to adjust the volume status and the dose of diuretic therapy in the routine follow-up of patients with heart failure. According to previous studies and our study results, >7 kPa value for liver stiffness determined in liver ultrasonography may be predictive for increased mean RAP[12].

The fibrosis-4 index is expressed as a cheap, easy, and simple index to evaluate liver stiffness, and liver fibrosis[13-15]. The fibrosis-4 index consists of four parameters. These parameters are aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and age[13-15]. Fibrosis-4 index formulated as = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count (109/L)](14). The fibrosis-4 index was stated to reflect liver stiffness/fibrosis associated with viral hepatitis of hepatitis C virus or human immunodeficiency virus infection and non-alcoholic fatty liver disease[13-15]. In studies conducted on patients with heart failure, it was found that fibrosis-4 index and all-cause mortality increased significantly as right atrial pressure and pro-brain natriuretic peptide increased[16-18]. Recently, the fibrosis-4 index is considered to be a surrogate marker to assess the prognosis and the severity of venous congestion in patients with heart failure[16-18]. In our study, we examined the relationships between the fibrosis-4 index and echocardiographic parameters, including estimated right atrial pressure, tricuspid valve regurgitation maximum velocity, inferior vena cava diameter, and collapsibility index.

2. Materials and methods

This study was conducted at a tertiary heart center between January 2021 and January 2023. A total of 127 patients with CHD were included in the study. 103 (81%) of these patients had atrial septal defect (ASD), 21 (20%) had ventricular septal defect (VSD), and 3 (3%) had patent ductus arteriosus (PDA). Of the patients with ASD, 90 (87%) were secundum type ASD, 11 (11%) were sinus venosus type ASD, and 2 (2%) were primum ASD. Patients with known acute or chronic liver disease, hepatitis, left-sided heart failure, significant left-sided valve insufficiency, obstructive and restrictive lung diseases, and use of liver toxic agents were not included in the study. Detailed medical records were reviewed and recorded. Blood samples of all patients were collected. Routine biochemical parameters, including liver function tests, were analyzed and recorded. The fibrosis 4 index was calculated. The fibrosis-4 index was calculated as follows: Fibrosis-4 index = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count (10^9/L)][14].

All patients underwent a comprehensive transthoracic echocardiography including two-dimensional and Doppler echocardiography. All patients were breathing spontaneously without mechanical ventilation and did not require vasopressor support. Images of the IVC were obtained via the subcostal window. Measurements were analyzed by a single operator with direct supervision by an echocardiographer who was blinded to clinical information. The echocardiographer was blinded to the fibrosis-4 index. From the apical approach, we measured tricuspid lateral annular systolic velocity (Sm), and the tricuspid annular plane systolic excursion (TAPSE) to assess right ventricular function. TAPSE was measured by the distance of the systolic excursion of the right ventricle annulus along its longitudinal plane using M-mode presentation in a right ventricle-focused apical 4-chamber view. Sm was measured by the velocity of the tricuspid lateral annular using Doppler tissue imaging in a right ventricle-focused apical 4-chamber view. The left ventricular ejection fraction (%) was measured by the modified Simpson technique using B-mode presentation in apical-2-chamber view and apical-4-chamber view. We also measured the peak early diastolic velocities (E), and the early diastolic myocardial velocities (Em) using general methods. The ratio of E and Em (E/Em) was calculated to estimate left ventricular filling pressures[19].

The IVC diameter was measured in the long axis within 1 to 2 cm of the junction with the right atrium during normal respiration as well as inspiratory sniff. The collapsibility index was calculated as; Collapsibility index = (Minimum IVC diameter during sniff / Maximum IVC diameter during normal respiration) X 100. Estimated RAP using the collapsibility index and maximum IVC diameter were used to categorize the patients into groups of increasing estimated RAP as defined by the 2019 American Society of Echocardiography guidelines[19,20]. If IVC diameter < 21mm and IVC collapsibility > 50%, the estimated right atrial pressure was evaluated as 3 mmHg (0-5), and if IVC diameter > 21 mm and IVC collapsibility < 50%, the estimated right atrial pressure was evaluated as 15 mmHg (10-20). In other cases, the estimated right atrial pressure was evaluated as 8 mmHg[5-10,19,20].

Doppler measurements were used to estimate systolic pulmonary artery pressure (PAP). Estimated systolic PAP was calculated by adding peak tricuspid regurgitation velocity and right atrial pressure. The simplified Bernoulli equation, estimated systolic PAP = 4(TRV max)2 + estimated mean RAP, was used (TRV max is the estimated Doppler peak velocity (m/s) across the tricuspid valve, provided there is no right ventricular outflow tract obstruction)[19,20].
TRV max value was used to estimate the probability of pulmonary hypertension (PH). If this value is less than ≤2.8 m/s or cannot be measured, then it is unlikely to suggest PH. If TRV max is between 2.9-3.4 m/s, the index of suspicion increases. This is even more likely if TRV max is >3.4 m/s without other signs of PH. The probabilities were then used to determine whether cardiac catheterization was necessary in individual patients[21,22].
All data were numerically encoded. For statistical analysis, they were entered into the SPSS 22.0 computer software package and scanned for variable and case-by-case missing values. Quantitative data were expressed as mean ± standard deviation. Qualitative data were compared between groups using the chi-square test. Pearson and/or Spearman correlation analyses were performed between

the fibrosis-4 index and echocardiographic parameters such as estimated RAP and TRV max, and correlation graphs were obtained. ROC curve analysis of TRV max and estimated RAP with Fibrosis-4 index was performed and graphs were obtained.

The Institutional Review Board of our Hospital approved this study (study approval number: 12-2020-2146). Written informed consent to participate in the study was obtained from all participants. The principles of the study are in accordance with the Declaration of Helsinki

3. Results

Table 1 shows the clinical characteristics of all patients. Study patients included 75 women (59%) with a mean age of 50 ± 9.9 years. Table 1 shows laboratory data from the day of admission. In our study, the fibrosis index 4 was significantly higher in increased estimated right atrial pressure, higher TRV max, increased estimated systolic pulmonary artery pressure, and increased IVC diameter. Fibrosis 4 index was significantly correlated with TRV max ($r = 0.51$, $p < 0.001$) (figure 1a), estimated right atrial pressure ($r = 0.63$, $p < 0.001$) (figure 1b), estimated systolic pulmonary artery pressure ($r = 0.42$, $p < 0.001$) (figure 1c), IVC diameter ($r = 0.62$, $p < 0.001$) (figure 1d), IVC collapsibility ($r = 0.464$, $p < 0.001$), and NT-proBNp value ($r = 0.624$, $p < 0.001$). The fibrosis 4 index was also significantly correlated with the degree of tricuspid valve insufficiency($r = 0.342$, $p < 0.001$), RV basal diameter ($r = 0.294$, $p = 0.001$), ASD diameter($r = 0.27$, $p = 0.002$), Qp/Qs ($r = 0.271$, $p = 0.003$). However; the fibrosis 4 index was not significantly correlated with high-sensitive troponin ($r = 0.11$, $p = 0.43$). The fibrosis 4 index greater than 1.07 was associated with high TRV max (TRV max > 3.4 m/s), with a sensitivity of 81 % and a specificity of 74 % (Area under the ROC curve= 0.84; $p<0.001$; 95% CI: 0.74-0.94) (Figure 2a).

Table 1

Baseline clinical characteristics of this study

Variables	*n* = 127
Age, years	50 ± 9.9
Female, n (%)	75 (59)
Body mass index, kg/m^2	22.9 ± 4.2
Systolic blood pressure, mmHg	121.8 ± 18.8
Heart rate, b.p.m.	69.3 ± 14.5
Hypertension, n (%)	15 (11.8)
Diabetes mellitus, n (%)	2 (1.6)
Atrial fibrillation, n (%)	6 (4.7)
Prior percutaneous coronary intervention, n (%)	3 (2.4)
Beta-blockers, n (%)	16 (12.6)
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, n (%)	7 (5.5)
Left ventricular ejection fraction, %	62.7 (55.9–68.6)
Early diastolic filling velocity/early diastolic velocity of the mitral annulus	5.4 (4.0–7.1)
Tricuspid annular plane systolic excursion, mm	21.5 ± 4.6
Tricuspid lateral annular systolic velocity, cm/s	12.2 (10.0–14.6)
Inferior vena cava diameter, mm	19.6 ± 3.4
Maximum tricuspid regurgitation jet velocity (TRV max), m/s	2.87 ± 0.48
Estimated systolic PAP, mmHg	40.2 ± 15.8
Qp/Qs	1.73 ± 0.48

Notes:Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).

Figure 1

Scatter-dot plot showing the correlation of fibrosis 4 index with TRV max (figure 1a), estimated right atrial pressure (figure 1b), estimated systolic pulmonary artery pressure (figure 1c) and IVC diameter (figure 1d), respectively.

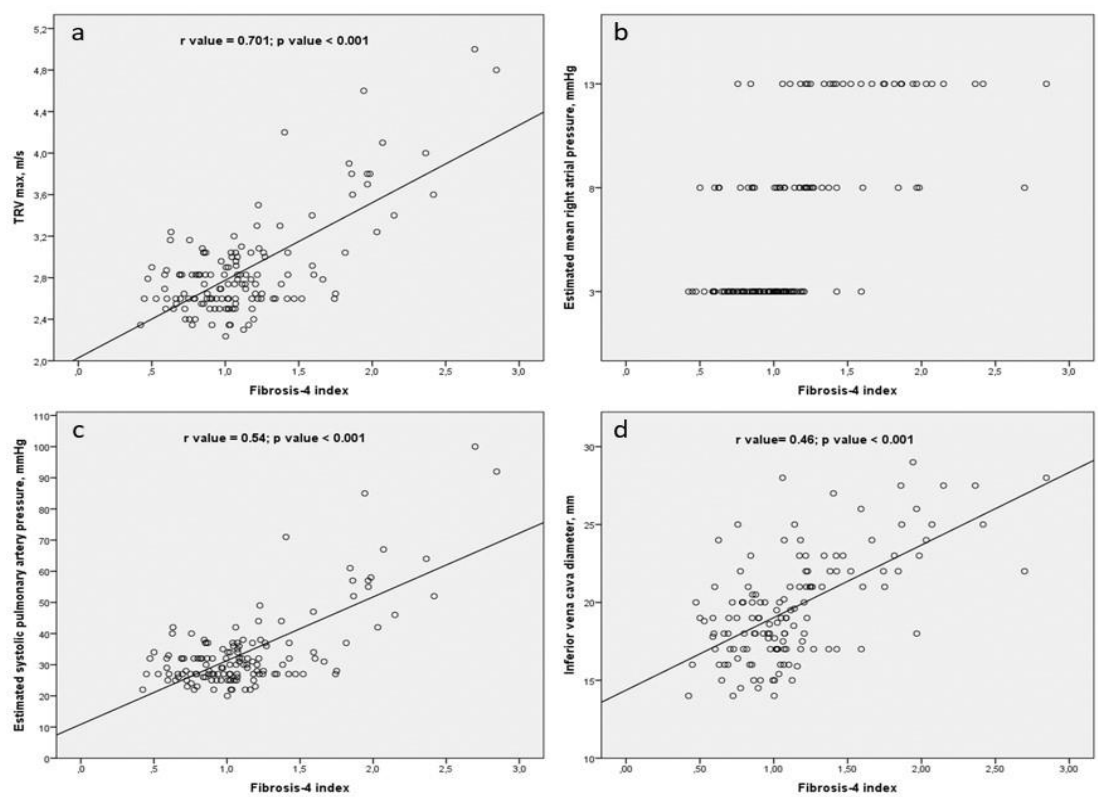
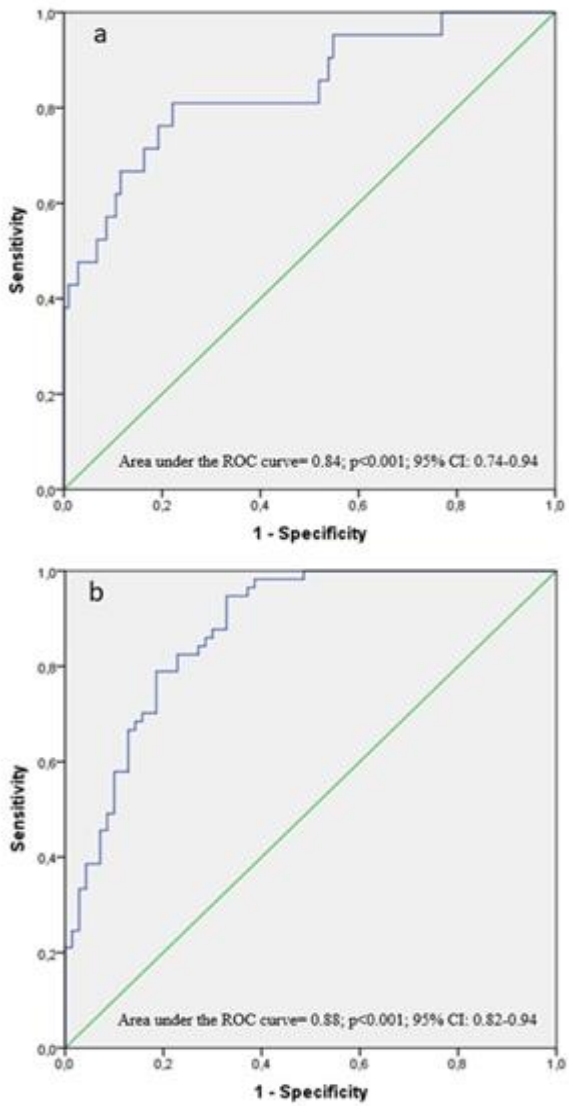


Figure 2

ROC analysis showing the relationship between fibrosis 4 index and TRV max (figure 2a), and estimated right atrial pressure (figure 2b), respectively.



The fibrosis 4 index greater than 1.23 was associated with increased estimated right atrial pressure (IVC diameter > 21mm and IVC collapsibility < 50%), with a sensitivity of 95 % and a specificity of 74 % (Area under the ROC curve= 0.88; p<0.001; 95% CI: 0.82-0.94) (Figure 2b).

The HALP score was statistically higher in NSTEMI group compared to NCA group (7.3 (5.1 – 10.0) for NSTEMI group and 5.1 (3.9 – 6.4) for NCA group, p<0.001). The main characteristics of the patient groups are shown in Table 1.

The binary logistic regression analysis was used to evaluate the impact of risk factors and laboratory parameters on NSTEMI patients. Age and HALP score have explanatory powers on NSTEMI patients (p=0.001 and p=0.022, in order of) (Table 2).

ROC curve analysis was formed to predict the best cut off value for HALP to predict NSTEMI in patients. The area under the curve was 0.706 which is an acceptable value. Best cut of value was 5.58 with 69.7% sensitivity and 62.5% specificity (Figure 2).

Table 2

Visual acuity and geriatric depression scale results before and after surgery

Variable	On admission
Haemoglobin, g/dL	12.4 ± 2.1
Platelet count, 109/L	264.3 ± 60.2
Prothrombin time, s	12.7 ± 2.3
Total Bilirubin, mg/dL	0.64 ± 0.32
Aspartate aminotransferase, IU/L	23.1 ± 7.1
Alanine aminotransferase, IU/L	17.9 ± 9.0
Fibrosis-4 index	1.13 ± 0.45
Total bilirubin, g/dL	0.8 (0.5–1.2)
Albumin, g/dL	42.7 ± 3.7
Serum creatinine, mg/dL	0.8 (0.5–1.1)
N-terminal pro-brain natriuretic peptide, pg/mL	700 (30–730)
High sensitivite troponin,	(1–48)

Notes:Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).

4. Discussion

In patients with CHDs, this study showed a significant correlation between the Fibrosis 4 index and echocardiographic estimated right atrial pressure (based on inferior vena diameter and collapsibility rate) or the estimated probability of pulmonary hypertension (based on TRV max) (figure 1, 2). In addition, the ROC analyses performed in this study found that the Fibrosis 4 index was quite sensitive and specific in showing echocardiographic increased right atrial pressure (via inferior vena diameter and collapsibility rate) or the possibility of high pulmonary hypertension (via TRV max) (figure 1, 2).

Liver tissue biopsy remains the reference standard for assessing the severity of diseases that directly or indirectly affect the liver. Currently, a variety of non-invasive methods are used to quantify liver fibrosis, including serum biomarkers and imaging techniques. Fibrosis-4 index, which is calculated with four parameters including age, ALT, AST, and platelet count, is among these methods. Fibrosis-4 index has been used as a surrogate marker of liver stiffness[14]. A recent comparative study by Forsgren MF and colleagues involving chronic liver diseases such as nonalcoholic fatty liver disease and chronic hepatitis C demonstrated that the diagnostic performance of magnetic resonance imaging, transient elastography, and fibrosis-4 index in predicting significant fibrosis was sufficiently accurate[23]. Therefore, the fibrosis-4 index may be a marker of liver fibrosis or stiffness in chronic liver disease.

The fibrosis-4 index is considered a simple biomarker of liver fibrosis in patients with liver diseases. However, the liver may become stiff because of long-term hepatic congestion and accompanying fibrosis in patients with ASD. Furthermore, liver stiffness measured by transient elastography increases as the central venous blood pressure increases[24].

Estimation of intravascular volume is very important, as it is a critical component for optimal patient care and management. RAP provides relevant clinicians with important information about their patients regarding the estimation of intravascular volume. Increased RAP is associated with adverse outcomes and is independently associated with all-cause mortality in patients with cardiovascular disease. The gold standard method for assessing RAP (or central venous pressure) remains invasive monitoring. However, various techniques are available for noninvasive evaluation of RAP. Various echocardiographic methods consisting of indices obtained from inferior vena cava diameter, inferior vena cava collapsibility index, hepatic veins, tissue Doppler parameters and right

atrial dimensions have been proposed for the noninvasive evaluation of RAP[25].

Jalal Z et al stated that liver stiffness measurement using Transient elastography is a rapid and reliable method to evaluate central venous pressure in patients with CHD. We compared the echocardiographic estimated RAP, which is an indirect indicator of invasively measured central venous pressure, which is an indicator of mean RAP, and the fibrosis 4 index, which can predict liver stiffness, and found that there is a significant relationship between these parameters[26].

PH occurs in approximately 10% of adult patients with CHD. PH is a relatively common complication in patients with CHD. PH in CHD patients is often associated with left-to-right shunt defects. Additionally, PH may develop secondary to left heart obstructive disease causing postcapillary hypertension in CHD[27]. Common congenital heart diseases include ASD, VSD, and PDA. PH and right heart failure are more common in ASD patients with large defects, undiagnosed for a long time, or without defect closure. Right ventricular dysfunction exacerbates the clinical findings of right heart failure. Sm and TAPSE are both indices of right ventricular contraction in the longitudinal plane. It provides sufficient data about right ventricle systolic dysfunction[28]. Saito Y et al demonstrated that liver stiffness, measured by transient elastography, increased with a decrease in TAPSE. They also demonstrated that a high fibrosis-4 index was associated with lower TAPSE and Sm. For this reason, the fibrosis-4 index can be regarded as a biomarker for right ventricular dysfunction in adult patients with ASD[29]. Our study showed that there is a significant relationship between TRV max and fibrosis-4, which contributes to predicting the possibility of PH echocardiographically. We also found that there was a correlation between estimated systolic pulmonary artery pressure and fibrosis-4 index. In our study, there were almost no patients with severe liver fibrosis/stiffness because the number of patients with severe right ventricular dysfunction or severe pulmonary arterial hypertension, including Eisenmenger syndrome, was very low. Examining this relationship in a large patient population, including patients with severe pulmonary arterial hypertension and/or right ventricular dysfunction in different types of CHD (sub)groups, may provide more accurate results. In a study published by Kerkütlüoğlu M., the fibrosis-4 index is stated as an independent prognostic indicator in pulmonary arterial hypertension patients. However, he claimed that the Fibrosis-4 index, a simple, cost-effective, and easily accessible tool, could be used to predict both survival rates and disease severity in individuals suffering from pulmonary arterial hypertension[30]. Although our study is not a prognosis study, the fibrosis-4 index may have prognostic value in congenital heart patients, as mean right atrial pressure and systolic pulmonary artery pressure have prognostic value in patients with pulmonary arterial hypertension. Further studies are required for this.

Limitation

This study had several limitations. First, this study was a retrospective cohort study at a single tertiary center, and the study had a relatively small sample size. Second, we did not perform additional examinations such as liver biopsy or computed tomography scans for evaluation. chronic liver diseases were not completely ruled out.

5. Conclusion

The fibrosis-4 index, which is a marker of liver congestion/stiffness/fibrosis, may be an important indicator in the echocardiographic determination of estimated mean RAP and the possibility of PH in patients with CHD. A more comprehensive study, including invasive right heart catheterization parameters and prognosis data, is needed to support these results.

Statement of ethics

The study was approved by the local ethics committee Hospital approved this study (study approval number: 12-2020-2146).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1.Weisberg IS, Jacobson IM. Cardiovascular Diseases and the Liver. Clinics in Liver Disease. 2011; 15(1): 1-20.
https://doi.org/10.1016/j.cld.2010.09.010
2.Asrani SK, Asrani NS, Freese DK, et al. Congenital heart disease and the liver. Hepatology. 2012; 56(3):1160-9.
https://doi.org/10.1002/hep.25692
3.Evlice M, Bedir Ö, Coşkun M, et al. The relationship between echocardiographic parameters and albumin bilirubin (ALBI) score in patients with isolated secundum type atrial septal defect. Echocardiography. 2023 Apr 1.
https://doi.org/10.1111/echo.15556
4.Engelings CC, Helm PC, Abdul-Khaliq H, et al. Cause of death in adults with congenital heart disease - An analysis of the German National Register for Congenital Heart Defects. Int J Cardiol 2016; 211: 31-6.
https://doi.org/10.1016/j.ijcard.2016.02.133
5.Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. N Engl J Med. 2013; 368: 1756-7.
https://doi.org/10.1056/NEJMc1214222
6.Correale M, Tarantino N, Petrucci R, et al. Liver disease and heart failure: Back and forth. Eur J Intern Med 2018; 48: 25-34.
https://doi.org/10.1016/j.ejim.2017.10.016
7. Alonso-Gonzalez R. Liver dysfunction and congenital heart disease: Are we ready for the epidemic? Int J Cardiol 2017; 249: 169-70.
https://doi.org/10.1016/j.ijcard.2017.08.050
8.Austin C, Alassas K, Burger C, et al. Echocardiographic Assessment of Estimated Right Atrial Pressure and Size Predicts Mortality in Pulmonary Arterial Hypertension. Chest. 2015; 147(1): 198-208.
https://doi.org/10.1378/chest.13-3035
9.Benza RL , Gomberg-Maitland M , Miller DP , et al . Th e REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension . Chest . 2012 ; 141 (2): 354 - 62 .
https://doi.org/10.1378/chest.11-0676
10.Farber HW , Foreman AJ , Miller DP , McGoon MD . REVEAL Registry: correlation of right heart catheterization and echocardiography in patients with pulmonary arterial hypertension . Congest Heart Fail . 2011; 17 (2): 56 – 64.
https://doi.org/10.1111/j.1751-7133.2010.00202.x
11.Prekker ME , Scott NL , Hart D , Sprenkle MD , Leatherman JW . Point-of-care ultrasound to estimate central venous pressure: a comparison of three techniques . Crit Care Med . 2013; 41(3): 833–41.
https://doi.org/10.1097/CCM.0b013e31827466b7
12.Demirtas AO, Koc AS, Sumbul HE, et al. Liver stiffness obtained by ElastPQ ultrasound shear wave elastography independently determines mean right atrial pressure. Abdom Radiol. 2019; 44: 3030-9.
https://doi.org/10.1007/s00261-019-02083-3
13.Aspromonte N, Fumarulo I, Petrucci L, et al. The Liver in Heart Failure: From Biomarkers to Clinical Risk. Int. J. Mol. Sci. 2023;24:15665.
https://doi.org/10.3390/ijms242115665
14.Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43: 1317-25.
https://doi.org/10.1002/hep.21178
15.Sumida Y, Yoneda M, Hyogo H, et al. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. BMC Gastroenterol. 2012; 12: 2.
https://doi.org/10.1186/1471-230X-12-2
16.Iwasaki Y, Tomiyama H, Shiina K, et al. Liver stiffness and arterial stiffness/abnormal central hemodynamics in the early stage of heart failure. Int J Cardiol Heart Vasc 2018; 20: 32-37.

https://doi.org/10.1016/j.ijcha.2018.07.001
17.Maeda D, Sakane K, Ito T, et al. Fibrosis-4 index reflects right-sided filling pressure in patients with heart failure. Heart Vessels 2020; 35: 376-83.
https://doi.org/10.1007/s00380-019-01505-y
18.Sato Y, Yoshihisa A, Kanno Y, et al. Liver stiffness assessed by Fibrosis-4 index predicts mortality in patients with heart failure. Open heart. 2017; 4: e000598.
https://doi.org/10.1136/openhrt-2017-000598
19.Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2019;32(1):1-64.
https://doi.org/10.1016/j.echo.2018.06.004
20.Evlice M, Kurt İH. Pulmoner Hipertansiyonda Transtorasik Ekokardiyografinin Yeri.
21.Evlice M, Kurt İH. "3. Sağ/Sol Kalp Kateterizasyonu ve Vazoreaktivite Testi."
22.Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). European heart journal. 2022;43(38): 3618-731.
23.Forsgren MF, Nasr P, Karlsson M, et al. Biomarkers of liver fibrosis: prospective comparison of multimodal magnetic resonance, serum algorithms and transient elastography. Scand J Gastroenterol 2020; 55: 848-59.
https://doi.org/10.1080/00365521.2020.1786599
24.Millonig G, Friedrich S, Adolf S, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010; 52: 206-10.
https://doi.org/10.1016/j.jhep.2009.11.018
25.Beigel R, Cercek B, Luo H, Siegel RJ. Noninvasive evaluation of right atrial pressure. Journal of the American Society of Echocardiography. 2013;26(9):1033-42.
https://doi.org/10.1016/j.echo.2013.06.004
26.Jalal Z, Iriart X, De Lédinghen V, et al. Liver stiffness measurements for evaluation of central venous pressure in congenital heart diseases. Heart. 2015;17.
https://doi.org/10.1136/heartjnl-2014-307385
27.Pascall E, Tulloh RM. Pulmonary hypertension in congenital heart disease. Future cardiology. 2018; 14(4): 343-53.
https://doi.org/10.2217/fca-2017-0065
28.Rudski LG, Lai WW, Lai AJ, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713.
https://doi.org/10.1016/j.echo.2010.05.010
29.Saito Y, Kato M, Nagashima K, et al. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. Circ J. 2018; 82: 1822-9.
https://doi.org/10.1253/circj.CJ-17-1344
30.Kerkütlüoğlu M. Fibrosis-4 Index as an Independent Predictor of Mortality in Pulmonary Arterial Hypertension. E Journal of Cardiovascular Medicine. 2023;11(3).
https://doi.org/10.32596/ejcm.galenos.2023.2023-2-11

Diabetic Foot: Wound Healing, Amputation Decision and Innovative Developments

Rana Kapukaya[1], Mehmet Bozkurt[2]

1 Health Science University Adana City Hospital Plastic Reconstructive & Aesthetic Surgery Department, Adana, Türkiye
2 Private Practice, Plastic Reconstructive and Aesthetic Surgery, İstanbul, Türkiye

Abstract

Aim: To review the effects of diabetes-related diseases on the healing process and amputation decision in diabetic foot ulcers (DFU), negative pressure wound therapy (NPWT) results, and current treatment approaches.

Methods: The study was planned as retrospective and cross-sectional. Data of patients who were admitted to our clinic due to DFU and were treated were examined. A total of 38 patients were included in the study. The results of patients (n=19) who underwent periodic debridement and classic dressing were compared with the results of patients (n=19) who underwent NPWT. Healing in patients was achieved by amputation (n=8), repair with partial thickness grafts or flaps (n=10), and secondary epithelialization development (n=10). The effect of diabetes-related peripheral arterial disease (PAD), cardiovascular disease (CVD), chronic kidney disease (CKD), diabetic retinopathy (DRP), and previous amputation history (AH) on recovery time was examined. The predictive importance of diabetes-related diseases for amputation was investigated.

Results: It was determined that diabetes-related diseases caused a delay in wound healing. [PAD ($p<0.044$), CVD ($p<0.016$), CKD ($p<0.001$), DRP ($p<0.001$)], The delay in wound healing was evident in the presence of CKD and DRP. Wound healing time was not affected in patients with AH ($p>0.05$). The incidence of PAD was higher in patients who underwent amputation. There was no significant difference between NPWT (mean 67 days) and the classic dressing group (mean 73 days) in terms of healing time ($p>0.05$).

Conclusions: In the presence of diabetes-related diseases, wound healing time was prolonged. This effect was more evident in the presence of DRP and CKD. This may be explained by microvascular disease, but larger series studies are needed. Wound healing was not affected in patients with AH. The incidence of PAD was found to be higher in patients who underwent amputation. Improving the care conditions of patients with diabetes and accessing treatment facilities will reduce DFU and amputation rates. No difference was found between NPWT and classic dressing in terms of healing time. However, it was observed that NBWT increased the development of granulation in the wound, reduction of edema, wound contraction, and the chance of success of the graft or flap surgery. Innovative studies are needed to develop optimum wound surfactant molecules in this regard.

Keywords: *Diabetic foot ulcer, wound healing, amputation, diabetes-related diseases*

1. Introduction

The main problem in the development of diabetic foot ulcer (DFU) is microangiopathy. DFU and lower extremity amputation (LEA) are independent risk factors associated with early death[1]. The 5-year survival rate in patients with diabetes who develop lower extremity complications is worse than in patients with many common types of cancer[2]. Duration of diabetes, glycemic control, and epigenetic features are the most effective factors in the development of complications[3]. The development of micro and macrovascular complications in diabetes is an independent risk factor in the development of DFU. Today, despite the advances made in elucidating the potential mechanisms underlying DFU (physiologic, pathologic, cellular, molecular signaling pathway, and epigenetics), the same parallelism has not been achieved in its treatment. The fact that the wound is associated with complex pathogenic factors makes the treatment difficult. Especially in a wound complicated by infection and combined with vascular insufficiency, the failure rate in treatment will increase if both infection and microvascular insufficiency cannot be managed simultaneously.

* Corresponding Author: Rana Kapukaya, e-mail: dr__rana@hotmail.com
Received: 13.12.2023, Accepted: 04.01.2024, Available Online Date: 01.03.2024
Cite this article as: Kapukaya R, Bozkurt M. Diabetic Foot: Wound Healing, Amputation Decision, and Innovative Developments. J Cukurova Anesth Surg. 2024; 7(1)): 23-6. https://doi.org/10.36516/jocass.1404365

Studies show that major amputations are not the solution. Therefore, wound care, which is the step before amputation, is very important for patients with diabetic foot. Developed as an alternative to traditional wound treatment, NPWT has made this process more transparent by understanding many mechanisms in wound healing. Studies have shown that NPWT increases granulation tissue, accelerates wound healing by increasing local blood flow, and removes exudate and proinflammatory cytokines from the environment. In wound healing, NPWT acts by causing contraction in the wound with negative pressure applied to the surface, protecting the wound from external micro-organisms, keeping the wound warm and moist, drawing exudate in the soft tissue, reducing edema in the wound, and increasing cellular proliferation[4].

The study aimed to investigate the effect of diabetes-related diseases (PAD, CVD, CKD, DRP), previous amputation history, and NPWT on the healing process and amputation decision.

2. Materials and methods

The study was planned as retrospective and cross-sectional. Information about patients who applied to our clinic due to diabetic foot between 2008 and 2011 was retrospectively reviewed. A total of 38 patients were included in the study.

Patients with a follow-up period of less than 1 year, oncology patients, patients with systemic connective tissue disease, patients receiving immunosuppressive therapy, and pregnant patients were excluded from the study.

Approval for the study was received from the ethics committee of our institution. Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The study was started after receiving ethics committee approval.

The patients' age, sex, duration of diabetes, recovery time, treatments administered, and presence of comorbid diseases were examined retrospectively. Data were accessed from the archive, patient files and information processing system.

Healing: Ensuring epithelial continuity with no discharge or signs of infection in the wound was considered as the absence of an open wound.

Peripheral artery disease (PAD): Ankle brachial index (ABI) less than 0.90.

Chronic kidney disease (CKD): Albuminuria greater than 30 mg/g creatinine and estimated glomerular filtration rate (tGFR) less than 60 mL/min/1.73.

Cardiovascular disease (CVD): Presence of hypertension, coronary artery disease, and heart failure.

Diabetic retinopathy (DRP): Monitoring the changes due to nonproliferative retinopathy within the borders of the retina and proliferative retinopathy extending into the vitreous during fundus examination.

History of amputation (AH): Major or minor limb loss in the lower or upper extremities at any stage of life in a patient with diabetes.

Negative pressure wound therapy (NBWT): This was applied to the wound after debridement and irregulation, if necessary, and NBWT changed every 3 days, until the wound was ready for surgery or until dermal healing was completed.

Classic dressing: After the necessary debridement and irregulation of the wound, dressings was changed daily and used until the wound was ready for surgery or until dermal healing was completed. Sterile gauze was applied to the wound surface after moistening it with isotonic solution.

2.1. Statistical Analysis

Normality control of continuous variables was evaluated using the Shapiro-Wilk test. The independent sample t-test was used in cases that showed normal distribution, and the Mann-Whitney U test was used in cases that did not. Fisher's exact test was used to analyze categorical data. The analysis of the data was evaluated in the Statistica version 13.5.0.17 program. The statistical significance level was accepted as 0.05.

3. Results

The average age of the patients included in the study was 53.6 (min 31–max 85) years. There were 14 female patients and 24 male patients. The average diabetes duration of the patients was 12.8 (range, 1 - 25) years.

There was a history of PAD in 39% of the patients, CVD in 65%, CKD in 42%, DRP in 63%, and AH in 21%. It was determined that the healing time (days) prolonged with the presence of PAD ($p<0.044$), DRP ($p<0.001$), CKD ($p<0.001$) and CVD ($p<0.016$). It was found that the delay in wound healing was quite evident in the presence of DRP and CKD. Wound healing time was not affected in patients with AH ($p>0.05$). (Table 1)

Table 1

Recovery times in the presence of diabetes-related diseases and amputation history

		n	Mean±SD	Median [IQR]	Min-Max	p
DRP	No	14	52.86±12.30	55 [41.25-65.5]	37-73	<0.001[a]
	Yes	24	73.08±13.36	73 [67-84.5]	35-90	
CKD	No	22	56.82±13.00	62.5 [42-67]	35-73	<0.001[a]
	Yes	16	77.75±11.78	80.5 [68.5-87]	46-90	
PAD	No	23	61.39±16.32	67 [42-73]	35-90	0.044[b]
	Yes	15	72.13±14.09	73 [67-87]	44-90	
CVD	No	13	56.23±16.37	60 [40.5-67]	37-85	0.016[a]
	Yes	25	70.52±14.10	67 [66-82.5]	35-90	
AH	No	30	65.03±16.77	67 [52.75-77.5]	35-90	0.665[b]
	Yes	8	67.88±14.55	67 [58-81]	42-87	

a:Mann-Whitney U test. B:Independent Samples t-test, IQR:Interquartile Range

Table 2

Amputation rates in diabetes-related diseases

		Amputation				Total		
		Yes		No				
		n	%	n	%	n	%	p
DRP	No	10	33.3	4	50.0	14	36.8	0.433
	Yes	20	66.7	4	50.0	24	63.2	
CKD	No	17	56.7	5	62.5	22	57.9	0.999
	Yes	13	43.3	3	37.5	16	42.1	
PAD	No	21	70.0	2	25.0	23	60.5	0.039
	Yes	9	30.0	6	75.0	15	39.5	
CVD	No	12	40.0	1	12.5	13	34.2	0.222
	Yes	18	60.0	7	87.5	25	65.8	

p: Fisher's exact test

Of the patients who underwent amputation (n=8), 50% had DRP, 37% had CKD, 75% had PAD, and 87.5% had CVD. When patients with and without amputation were compared, it was determined that PAD was important in the amputation decision (p=0.039). (Table 2)

In terms of healing time, the difference between NPWT (mean 67 days) and the classic dressing group (mean 73 days) was not significant (p>0.05). However, a significant reduction in extremity edema was observed in patients who underwent NPWT. Macroscopically, an increase in wound contraction and granulation tissue was observed. (Table 3)

Table 3

Healing time NPWT and classic dressing

	n	Mean±SD	Median [IQR]	Min-Max	p
NBWT	19	68.79±9.43	67 [67-67]	55-90	0.665
Classic dressing	19	62.47±20.7	73 [42-83]	35-89	

p:Mann-Whitney U test, IQR:Interquartile Range

4. Discussion

It is known that the prevalence of PAD in diabetes is between 20% and 50%[5]. In studies, PAD has been found to be associated with delayed wound healing, infection and increased amputation rates[6-7]. When patients with and without amputation were compared, it was understood that the presence of PAD was important in the decision for amputation. The predictive importance of PAD for amputation can be more clearly understood through larger series of studies. However, it was seen that wound healing was delayed in the presence of PAD.

In prospective clinical studies, CVD has been associated with severe DRP, end-stage CKD, delayed healing of ischemic ulcers, rapid progression, amputation, and mortality[8]. In our study, it was determined that DFU recovery time (days) increased in the presence of diabetes-related PAD, DRP, CVD, and CKD. This effect was quite evident in the presence of DRP and CKD. This result may be explained by microvascular disease because microvascular disease associated with diabetes is pathognomic, especially in the development of DRP and CKD, and is important in predicting prognosis[9]. No information could be found in the literature regarding the risk of microvascular disease and DFU development and its predictive importance for amputation.

The lifetime risk of lower extremity amputation in patients with diabetes is approximately 25%[10]. In our study, the prevalence of amputation was 21%. The presence of diabetes-related PAD, DRP, CVD, and CKD creates an increased risk for foot ulcers and lower extremity amputations. These data was supported by the results of our study. In our study, the incidence of PAD was found to be high in patients with AH.

Studies have shown that the greatest risk for amputation is low socioeconomic status and poor self-care[11]. The strongest clinical indicator in the development of DFU is the presence of a previous foot ulcer or AH[12]. However, there is no information about whether it affects the healing time. We determined that the wound healing rate was not affected in patients with AH.

The most important factor playing a role in diabetic wound pathology is cellular aging. Senescent cells have a phenotype that produces a secretome rich in pro-inflammatory cytokines and tissue-degrading proteases. Chronic wound microenvironment, high levels of inflammation, and oxidative stress induce cell aging[13]. Applying negative pressure to the wound appears to be very effective in restructuring cells, ensuring matrix regeneration, and removing inflammation mediators from the environment. However, there is no consensus on the effectiveness of NPWT in the treatment of DFU.

There are studies indicating that it does not contribute to shortening recovery time. On the other hand, there are also studies indicating that NPWT shortens the recovery period, but is not cost-effective[14]. Some studies report that it increases the granulation tissue and increases the chance of graft success in post-graft application[15]. One of the aims of NPWT is to prepare the wound for surgery as soon as possible. The clinically expected result may not be complete wound closure. It is an intermediate step in completely closing the wound and aims to shorten the hospital stay[16].

In our study, no statistically significant difference was found between the NPWT group (mean days) and the classic dressing group (mean days) in terms of recovery time (p>0.05). Negative pressure applied physically to the wound at optimum pressure and frequency reduces the bacterial load by drawing exudate. However, the most important parameter of NPWT's antibacterial effect is the surface contact material. Polyurethane sponge containing silver nitrate is frequently used. In studies conducted on this subject, the results of using polyurethane sponges containing boric acid as wound contact material in NPWT are remarkable. Innovative developments in wound healing have shown that boric acid is an effective molecule, especially in chronic wounds[17].

5. Conclusion

As a result of our study, diabetes-related diseases prolonged the recovery time of wound healing. The presence of DRP and CKD prolonged the healing time the most. It was understood that the recovery time was not affected in patients with AH. However, the incidence of PAD was found to be high in patients who underwent amputation. NPWT did not affect the healing rate in DFU. However, decreased edema, increased granulation, and contraction effects on the wound were observed. DFU is a preventable disease. The socioeconomic conditions of patients with diabetes should be improved and the conditions for accessing care facilities should be regulated. Finally, funds allocated for DFU research are insufficient. In this regard, innovative studies on wound healing should be supported.

Statement of ethics

The study was approved by the local ethics committee (ESH/GOEK 2011/206).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=zqI_ZOq-b18GC2rT9c2JGtl2C11pLEGOl5TDEodgEkzm6fOCeBibKrXiwqD1H6Au
Thesis number: 298937 Dicle University

References

1.Chen L, Sun S, Gao Y, Ran X. Global mortality of diabetic foot ulcer: a systematic review and meta-analysis of observational studies. Diabetes Obes Metab. 20 August 2022 [Epub ahead of print].
https://doi.org/10.1111/dom.14840

2.Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res 2020;13:16. https://doi.org/10.1186/s13047-020-00383-2
3.D Haibo, L Binghui, S Qian Shen, Z Chenchen, K Liwen, C Ran, W SiYuan, et al. Mechanisms of diabetic foot ulceration: A review. Journal of Diabetes.2023;15:299–312. https://doi.org/10.1111/1753-0407.13372
4.Orgill DP, Manders EK, Sumpio BE, et al. The mechanisms of action of vacuum assisted closure: More to learn. Surgery. 2009; 146:40–51. https://doi.org/10.1016/j.surg.2009.02.002
5.Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. Arterioscler Thromb Vasc Biol 2020; 40:1808–17. https://doi.org/10.1161/ATVBAHA.120.314595
6.Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008; 51: 747–55. https://doi.org/10.1007/s00125-008-0940-0
7.Newhall K, Spangler E, Dzebisashvili N, et al. Amputation rates for patients with diabetes and peripheral arterial disease: the effects of race and region. Ann Vasc Surg 2016; 30: 292–298.e1 https://doi.org/10.1016/j.avsg.2015.07.040
8.Zhang Y, Cramb S, McPhail SM, et al.; Diabetic Foot Working Group, Queensland Statewide Diabetes Clinical Network, Australia. Factors associated with healing of diabetesrelated foot ulcers: observations from a large prospective real-world cohort. Diabetes Care 2021;44:e143–e145. https://doi.org/10.2337/dc20-3120
9.Violetta JL, Kartasasmita AS, Supriyadi Ret al. Circulating Biomarkers to Predict Diabetic Retinopathy in Patients with Diabetic Kidney Disease. Disease. Vision 2023, 7, 34. https://doi.org/10.3390/vision702003
10.Centers for Disease Control and Prevention. National Diabetes Statistics Report. Atlanta, GA, Centers for Disease Control and Prevention, 2022. Accessed 6 June 2022. Available from;İ www.cdc.gov/diabetes/data/statistics-report/index.html
11.Zhang GQ, Canner JK, Kayssi A, et al. Geographical socioeconomic disadvantage is associated with adverse outcomes following major amputation in diabetic patients. J Vasc Surg 2021; 74: 1317–1326.e1. https://doi.org/10.1016/j.jvs.2021.03.033
12. Hicks CW, Canner JK, Mathioudakis N, et al. Incidence and risk factors associated with ulcer recurrence among patients with diabetic foot ulcers treated in a multidisciplinary setting. J Surg Res 2020;246: 243–50. https://doi.org/10.1016/j.jss.2019.09.025
13.Chen J, Qin S, Liu S, Zhong K, Jing Y, Wu X, Peng F, Li D and Peng C (2023) Targeting matrix metalloproteases in diabetic wound healing. Front. Immunol. 14:1089001. https://doi.org/10.3389/fimmu.2023.1089001
14.Chen C, Yi Lu, Hsieh CH, et al. Advanced Biomaterials and Topical Medications for Treating Diabetic Foot Ulcers: A Systematic Review and Network Meta-Analysis.Advances in Wound Care. http://doi.org/10.1089/wound.2023.0024
15.Topuz S, Ciger A, Isler A, Alkan M. Effects of negative pressure wound therapy on graft success in patients with diabetic foot ulcers: A retrospective study. Ann Med Res. 2023;30(8):846–50. https://doi.org/10.5455/annalsmedres.2023.02.040
16.Quacinella MA, Yong TM, Obremskey WT, Stinner DJ. Negative pressure wound therapy: Where are we in 2022? OTA Int. 2023;11:e247. https://doi.org/10.1097/OI9.0000000000000247
17.Kapukaya, R, Ciloglu, O. Treatment of chronic wounds with polyurethane sponges impregnated with boric acid particles: A randomised controlled trial. Int Wound J. 2020; 17: 1159–1165. https://doi.org/10.1111/iwj.13463

Treatment of Grade 3 Hallux Rigidus Cases: Distal Metatarsal Dorsiflexion Osteotomy Combined with Cheilectomy Short-Term Period Radiological and Clinical Outcomes

Mehmet Yiğit Gökmen [1], Mesut Uluöz[1]

1 Department of Orthopedics and Traumatology, Adana City Training and Research Hospital, Adana, Türkiye

Abstract

Aim: The aim of the study was to analyze the short-term radiological and clinical results of the distal metatarsal dorsiflexion osteotomy method, a technique used to preserve the joint in grade 3 hallux rigidus cases.

Methods: The retrospective study was conducted at Adana City Training and Research Hospital between January 2018 and January 2023. The analysis included adult cases with hallux rigidus grade 3, in whom at least six months of conservative treatment was unsuccessful and treated by distal metatarsal osteotomy combined with cheilectomy surgery. Age, gender, preoperative Coughlin and Shurnas grading scores, the functional clinical assessments were performed using the American Orthopaedic Foot and Ankle Society (AOFAS) Hallux score and Foot and Ankle Ability Measurement (FAAM) scores were assessed, the method of surgery, and complications were noted.

Results: The mean age of the study group (n=12) was 54.2±8.7, with ages varying between 44 and 68 years. The final assessments of the angle of the motion of the big toe showed that dorsiflexion, plantar flexion, and total motion values were significantly increased compared to the preoperative measurements, but between the sixth and the twelfth month, all three angles were decreased ($p<0.001$). Among all cases, mean AOFAS Hallux and FAAM Daily scores were significantly improved ($p <0.001$). The radiological assessment results of the first MTP joint showed that the final mean width was significantly increased compared to the preoperative measurement; however, the value was decreased compared to the sixth month ($p <0.001$).

Conclusions: In the surgical treatment of grade 3 hallux rigidus, distal metatarsal dorsiflexion osteotomy combined with cheilectomy increases the range of motion of the first MTP and provides clinical and radiological improvement. However, careful assessment is required before planning distal metatarsal dorsiflexion osteotomy based on the results of the studies conducted on hallux rigidus patients graded other than 3. Also, an intraoperative finding of a 50% intact cartilage rate or more should be considered as a motivating indicator for the surgeon.

Keywords: *Hallux, Rigidus, distal metatarsal osteotomy, first metatarsophalangeal joint, cheilectomy*

1. Introduction

Hallux rigidus is a frequently occurring joint inflammation pathology of the foot. The degenerative osteoarthritic changes in the first metatarsophalangeal (MTP) joint are characterized by dorsal and peripheral osteophyte formation, levelling of the metatarsal head, and lessened articular gap, causing widespread pain, dorsal tenderness, and joint stiffness with markedly reduced dorsiflexion[1,2]. Although the etiology of hallux rigidus remains unclear, it is linked to female gender, genealogical presence, hallux valgus interphalangeus, and particularly in cases with unilateral involvement with trauma history[3,4]. It is more common in middle-aged and older people, with an increased incidence in women around the age of 40 years[5,6].

Early classifications based on the radiological findings included three grades; later, Coughlin and Shurnas added symptoms and range of motion and developed the classification commonly used today[4,7].

In the initial stages of the disease, conservative methods and shoe modifications are mostly preferred in the treatment, but surgery is

Corresponding Author: Mehmet Yiğit Gökmen, mehmet_yigit_gokmen@hotmail.com, *Received: 21.12.2023, Accepted: 08.01.2024, Available Online Date: 01.03.2024 Cite this article as: Gökmen MY, Uluöz M. Treatment of Grade 3 Hallux Rigidus Cases: Distal Metatarsal Dorsiflexion Osteotomy Combined with Cheilectomy Short-Term Period Radiological and Clinical Outcomes. J Cukurova Anesth Surg. 2024; 7(1)): 27-31. https://doi.org/10.36516/jocass.1408096*

required for advanced cases, and many methods have already been described. Commonly used surgical treatment methods include cheilectomy, distal metatarsal osteotomy, proximal phalanx osteotomy, arthroplasty without or with implants, and arthrodesis.

Cheilectomy is one of the more commonly used surgical techniques that can also be used in the early stages. Sidon et al.[8] claimed in 2019 that cheilectomy was successful in grades 1-3. In patients with grade 3 and more than 50% intact cartilage in the distal metatarsal, osteotomies of the distal metatarsal or proximal phalanx are recommended[9,10]. Metatarsal osteotomy technique aims to conserve the first MTP joint and are recommended for light to average hallux rigidus deformities. The design aims to depressurize the joint by lessening the metatars bone or revolving the plantar cartilage of the first metatarsal head more caudally to articulate with the hallux[11].

Recently, several reports highlighted satisfactory clinical results in curing hallux rigidus using joint decompression techniques combined with osteotomy of the distal metatarsal and cheilectomy[12,13]. In advanced stages of hallux rigidus, such as in Grade 4 cases which lack articular cartilage, arthrodesis or arthroplasty is an option, but as many articles have shown, arthrodesis is considered the gold standard[4,14].

There are many studies in which all of these surgical treatment options have been successfully demonstrated. In this study, we aimed to compare the radiological and functional results of patients with stage 3 hallux rigidus who underwent joint decompression surgery with distal metatarsal osteotomy combined with cheilectomy in our clinic.

2. Materials and methods

2.1. Patients and Methods

The retrospectively designed study was carried out at Adana City Training and Research Hospital between January 2018 and January 2023. The analysis included adult cases with hallux Rigidus stage 3, in whom at least six months of conservative treatment was unsuccessful and treated by distal metatarsal osteotomy combined with cheilectomy surgery. Age, gender, preoperative Coughlin and Shurnas grading scores, the functional clinical assessments were performed using the American Orthopaedic Foot and Ankle Society (AOFAS) Hallux score and Foot and Ankle Ability Measurement (FAAM) scores were assessed, the method of surgery, and complications were noted. The measurements of the first metatarsophalangeal joint distance in the weight-bearing anteroposterior x-rays of the foot were performed preoperatively during the early postoperative period and at 6 and 12 months after surgery. The assessment of the range of motion, the AOFAS, and the FAAM scores were noted preoperatively and at 6 and 12 months after surgery. The early postoperative period was defined as the time between the second week and the third week following the surgery.

Patients with hallux rigidus developed due to rheumatoid arthritis, gout, fracture sequelae, or septic arthritis, patients with previous hallux valgus surgery, and patients not having a follow-up records of one year or more were excluded from the analysis.

2.2. Ethics

The ethical approval was provided by the Clinical Research Ethics Committee of the Adana City Training and Research Hospital on November 23, 2023, with decision number 2960.

2.3. Operative Technique

The surgical technique in distal metatarsal osteotomy combined with cheilectomy surgery patients was performed as follows: A 4 cm linear incision was cut starting from the dorsal side of the first MTP joint, continuing proximally from the joint border to the metatarsal neck, and a cheilectomy was performed. A 5 mm wide dorsal closed wedge dorsiflexion osteotomy was applied, beginning approximately 10 mm proximally from the top of the metatarsal head. The first osteotomy was made beginning from the dorsal to the plantar vertically (crossways to the axis of the first metatarsal), and the second cut was performed at a 60-degree angle to the metatarsal axis (practically dorsal-proximal to plantar-distal). The dorsal wedge was then removed, and the osteotomy topsides were closed. Since the distal part that included the joint surface was revolved dorsally and proximally, the undamaged cartilage surface in the plantar region of the metatarsal head touched the base of the proximal phalanx. After temporary fixation using two K-wires, the movement ability of the MTP joint and the stability of the osteotomy site were evaluated by using intraoperative fluoroscopy. Then, two headless titanium cannulated screws were placed retrogradely from the dorsal face in the direction of the plantar cortex vertical to the osteotomy surface. The entry points of the screws were positioned on the chondral surface of the dorsal side of the metatarsal head. The insertion depth was carefully measured preventing piercing the articular surface. Finally, the K-wires were disconnected, and the dorsal capsule was closed with an absorbable suture.

2.4. Postoperative Management

Patients were allowed to walk weight-bearing with a hard-soled shoe on the third postoperative day. Active and passive toe movement exercises were started at two weeks, and full weight-bearing walking and wearing casual or regular shoes were allowed at six weeks.

2.5. Radiologic and Clinical Evaluation

In the radiological evaluation of the patients, the first MTP joint distance was measured and recorded according to the method defined by Coughlin and Shurnas[4] as the distance from the articular surfaces of the base of the proximal phalanx to the apex of the metatarsal head. The first MTP joint space width measurements on weight-bearing anteroposterior foot radiographs were recorded preoperatively, in the early postoperative period, and at six months and 12 months postoperatively. All measurements were repeated three times by two orthopaedic surgeons, and the mean measurements were recorded.

AOFAS is a scale ranging from 0 to 100, with 100 points indicating the possibility of a patient feeling zero pain, complete sagittal and hindfoot movement capability, total ankle or hindfoot stability, no poor adjustment, able to ambulate more than six blocks and on various walking surfaces, not having perceptible limp, not having any restrictions of daily or recreational activities, and not requiring aids or appliances for walking. The score distribution of subdomains of function, pain, and alignment were 50, 40, and 10, respectively[15].

FAAM is a self-reported scale scoring from zero to 100 that assesses activities of daily life with 21 questions and sports with eight questions.[16]

The angle of motion of the big toe was quantized using a goniometer as defined by Ronconi et al.[13] preoperatively and six and 12 months postoperatively.

2.6. Statistical Analysis

The statistical analysis was performed using the statistical package SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). In assessing normal continuous variables, mean±standard deviation ($p>0.05$ in Shapiro-Wilk ($n<30$)), and for the abnormal continuous variables median were used for description. Data commands were used to calculate prevalence. Pre-post measures data were analyzed by the Friedman test and Wilcoxson test. The level of statistical significance was set as $p < 0.05$.

Table 1

Mean Passive Range of Motion of the First MTP Joint

	Preoperative		Postoperative six months		Postoperative one year		
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
Dorsiflexion	15.5˚±1.9˚	12˚-19˚	37.7˚±5.3˚	24˚-44˚	34.7˚±5.8˚	21˚-42˚	0.001
Plantar Flexion	20.9˚±1.9˚	18˚-25˚	23.3˚±2.4˚	20˚-28˚	21.3˚±1.7˚	18˚-24˚	0.001
Total Motion	36.0˚±2.7˚	30˚-40˚	60.7˚±6.9˚	44˚-70˚	56.2˚±7.4˚	39˚-65˚	0.002

Table 2

Evaluation of Clinical Outcomes Based on the American Orthopaedic Foot and Ankle Society Scale and Functional Outcomes Based on the Foot and Ankle Ability Measure

	Preoperative		Postoperative six months		Postoperative one year		
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
AOFAS Hallux Score	56.2±3.0	52-60	87.9±3.6	85-95	89.2±5.1	85-95	0.002
FAAM Daily Activity Score	66.3±5.2	58.3-75	84.2±3.9	79.8-91.6	90.6±2.4	86.9-94.1	0.001

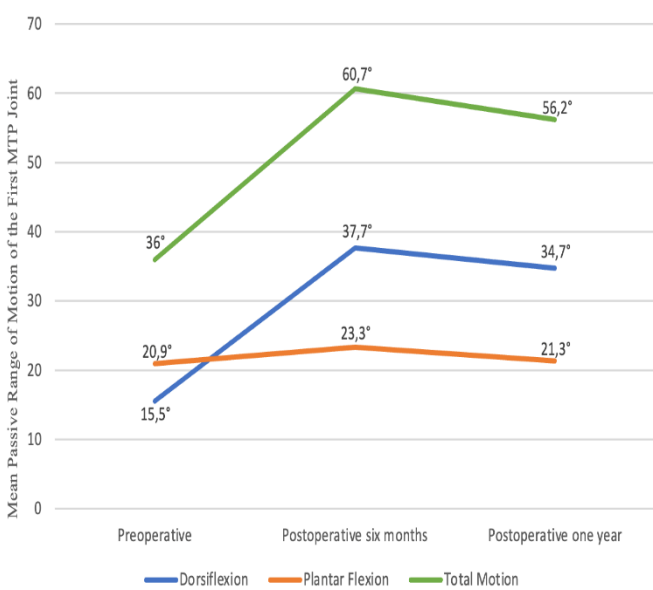
Table 3

The Changes in Width of the First MTP Joint Space

	Preoperative		Early Postoperative		Postoperative six months		Postoperative one year		
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
Width of the First MTP (mm)	0.76±0.1	0.55-0.96	1.48±0.1	1.29-1.78	1.29±0.1	1.02-1.46	1.15±0.1	0.88-1.33	0.001

Figure 1

The changes of mean passive range of motion of the first MTP joint in one year follow-up period



3. Results

The mean age of the study group (*n*=12) was 54.2±8.7, with ages varying between 44 and 68 years. There were eight females and four males. All cases were grade 3 based on the Coughlin and Shurnas clinical and radiographical grading system.

The final assessments of the angle of the motion of the big toe showed that dorsiflexion, plantar flexion, and total motion values were significantly increased compared to the preoperative measurements, but between the sixth and the twelfth month, all three angles were decreased (p<0.001). (Table 1) (Figure1)

Among all cases, mean AOFAS Hallux and FAAM Daily scores were significantly improved (p <0.001). (Table 2)

The radiological assessment results of the first MTP joint showed that the final mean width was significantly increased compared to the preoperative measurement; however, the value was decreased compared to the sixth month (p <0.001). (Table 3)

Postoperatively, transverse metatarsalgia was seen in two cases in the sixth month of follow-up control (16.7%). Metatarsal silicone pad and non-steroid analgesic treatment were applied. The findings were resolved at the final follow-up.

Additional complications, including non-union, loss of sensation due to digital nerve damage, implant failure, local wound infection, and irritation, were not observed.

4. Discussion

The aim of the study was to analyze the short-term clinical results of the distal metatarsal dorsiflexion osteotomy method, a technique used to preserve the joint in advanced hallux rigidus cases.

The literature findings suggest that the application of arthrodesis in hallux rigidus cases is more widely accepted compared to cheilectomy, osteotomy, implant arthroplasty, interposition arthroplasty, and resection arthroplasty[17].

There are numerous reports highlighting the effectiveness of the first MTP joint decompression osteotomy surgery in grade II and III hallux Rigidus cases[12,13,18]. The fact that the most important condition for the procedure is the preservation of the cartilage over 50% is commonly suggested in the literature[4,19]. All cases in the study group were assessed intraoperatively, and it was seen that the ratio of intact cartilage in the study group was over 50%.

In order to avoid the progression of the degenerative arthritis of the first MTP joint in advanced hallux rigidus patients, the dorsal closed wedge osteotomy, which was modified by Cho et al.[9] and considered as an alternative among numerous techniques that exist in the literature, was preferred aiming to increase the joint range of motion by rotating the intact cartilage on the plantar side of the metatarsal head and widening the joint width. Although the technique seems to offer upsides regarding providing adequate joint congruency along the range of motion in the first MTP joint and the facilitation of the excision of the pathological dorsal part of the joint, might increase the risk of an impairment in the adaptability of the sesamoids to the joint due to the rotation of the plantar side of the joint to the anterior.

A systemic review of the distal metatarsal periarticular osteotomy series showed that metatarsalgia was seen in 30.5% of the cases[20]. A lower rate was observed in our study group (n=2, 16.7%). The low rate seen in our study might be attributed to more detailed preoperative planning, including the consideration of the length of the metatarsal regarding the preservation of the metatarsal arcus, which is highly associated with decreased metatarsalgia following distal metatarsal osteotomy.

In a study presenting the long-term results of combined surgery methods, including cheilectomy and the proximal phalangeal osteotomy, which the latter is known to be one of the joint-preserving osteotomies preferred in hallux rigidus patients, and conducted on 60 cases with an average follow-up of 96 months, Waizy et al.[21] proposed that none of the cases required revision surgery.

Furthermore, in a review, Roukis[20] stated that in hallux rigidus patients the incidence of revision surgery following cheilectomy is relatively low (8.8%), and the leading cause of the revision surgery was the progressive arthritis of the first MTP joint. Besides, in the studies focused on long-term follow-ups after cheilectomy, the clinical impact of the recurrence of the dorsal osteophytes, chondrolysis, narrowing of the joint space, and the progression of the radiological grading of the condition was not proven on the function of the first MTP joint[22].

Yet again, according to Roukis[20] the main reasons for the revision surgery following periarticular osteotomy were persistent metatarsalgia, implant failures or irritations, and the progression of the degenerative arthritis on the first MTP joint. Adding that, based on high rates of revision, periarticular osteotomy shall be excluded from consideration as a first-line method regardless of the stage of the condition. The contradicting results on the complication rates of periarticular osteotomy in hallux rigidus surgery existing in the literature indicate the need for further studies with long-term follow-up.

Similar to the reports in hallux rigidus cases showing the lack of an association between a decrease in the dorsiflexion function and the radiologic findings, in our study, there was no relation[4]. Moreover, Coughlin and Shurnas[4] suggested that cheilectomy was not associated with the natural progress of the condition, and yet the patients have expressed satisfaction after the procedure. In another study, the authors stated that following a cheilectomy, there was no link between the AOFAS scores and the poor radiologic progress of the first MTP joint[23].

Limitations

A small sample size, having been conducted in a single center, and the lack of a control group are the major limitations of the study. Prospective randomized studies with longer follow-up periods comparing the most commonly used periarticular osteotomy procedures surely will help determine the most effective operation methods in patients with hallux rigidus grade 3.

5. Conclusion

In the surgical treatment of grade 3 hallux rigidus, distal metatarsal dorsiflexion osteotomy combined with cheilectomy increases the range of motion of the first MTP and provides clinical and radiological improvement. However, careful assessment is required before planning distal metatarsal dorsiflexion osteotomy based on the results of the studies conducted on hallux rigidus patients graded other than 3. Also, an intraoperative finding of a 50% intact cartilage rate or more should be considered as a motivating indicator for the surgeon.

Statement of ethics

The ethical approval was provided by the Clinical Research Ethics Committee of the Adana City Training and Research Hospital on November 23, 2023, with decision number 2960.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1.McMaster M. The pathogenesis of hallux rigidus. The Journal of Bone and Joint Surgery British volume. 1978; 60(1): 82–7. https://doi.org/10.1302/0301-620X.60B1.627584

2.Deland JT, Williams BR. Surgical Management of Hallux Rigidus: Journal of the American Academy of Orthopaedic Surgeons. 2012; 20(6): 347–58. https://doi.org/10.5435/JAAOS-20-06-347

3.Cotterill JM. Stiffness of the Great Toe in Adolescents. BMJ. 1887; 1(1378): 1158–1158. https://doi.org/10.1136/bmj.1.1378.1158

4.Coughlin MJ, Shurnas PS. Hallux rigidus. Grading and long-term results of operative treatment. J Bone Joint Surg Am. 2003; 85(11): 2072–88.

5.Shereff MJ, Baumhauer JF. Current Concepts Review - Hallux Rigidus and Osteoarthrosis of the First Metatarsophalangeal Joint*: The Journal of Bone & Joint Surgery. 1998; 80(6):898–908. https://doi.org/10.2106/00004623-199806000-00015

6.Polzer H. Hallux rigidus: Joint preserving alternatives to arthrodesis - a review of the literature. WJO. 2014; 5(1): 6. https://doi.org/10.5312/wjo.v5.i1.6

7.Hattrup SJ, Johnson KA. Subjective results of hallux rigidus following treatment with cheilectomy. Clin Orthop Relat Res. 1988; (226): 182–91.

8.Sidon E, Rogero R, Bell T, McDonald E, Shakked RJ, Fuchs D, et al. Long-term Follow-up of Cheilectomy for Treatment of Hallux Rigidus. Foot Ankle Int. 2019; 40(10): 1114–21. https://doi.org/10.1177/1071100719859236

9.Cho BK, Park KJ, Park JK, SooHoo NF. Outcomes of the Distal Metatarsal Dorsiflexion Osteotomy for Advanced Hallux Rigidus. Foot Ankle Int. 2017; 38(5): 541–50.
https://doi.org/10.1177/1071100716688177
10.Maes DJA, De Vil J, Kalmar AF, Lootens T. Clinical and Radiological Outcomes of Hallux Rigidus Treated With Cheilectomy and a Moberg-Akin Osteotomy. Foot Ankle Int. 2020; 41(3): 294–302.
https://doi.org/10.1177/1071100719897264
11.Kilmartin TE. Phalangeal osteotomy versus first metatarsal decompression osteotomy for the surgical treatment of hallux rigidus: a prospective study of age-matched and condition-matched patients. J Foot Ankle Surg. 2005; 44(1): 2–12.
https://doi.org/10.1053/j.jfas.2004.11.013
12.Lundeen RO, Rose JM. Sliding oblique osteotomy for the treatment of hallux abducto valgus associated with functional hallux limitus. J Foot Ankle Surg. 2000; 39(3): 161–7.
https://doi.org/10.1016/s1067-2516(00)80017-4
13.Ronconi P, Monachino P, Baleanu PM, Favilli G. Distal oblique osteotomy of the first metatarsal for the correction of hallux limitus and rigidus deformity. J Foot Ankle Surg. 2000; 39(3): 154–60.
https://doi.org/10.1016/s1067-2516(00)80016-2
14.Galois L, Hemmer J, Ray V, Sirveaux F. Surgical options for hallux rigidus: state of the art and review of the literature. Eur J Orthop Surg Traumatol. 2020; 30(1): 57–65.
https://doi.org/10.1007/s00590-019-02528-x
15.Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int. 1994; 15(7): 349–53.
https://doi.org/10.1177/107110079401500701
16.Martin RL, Irrgang JJ, Burdett RG, Conti SF, Van Swearingen JM. Evidence of validity for the Foot and Ankle Ability Measure (FAAM). Foot Ankle Int. 2005; 26(11): 968–83.
https://doi.org/10.1177/107110070502601113
17.McNeil DS, Baumhauer JF, Glazebrook MA. Evidence-based analysis of the efficacy for operative treatment of hallux rigidus. Foot Ankle Int. 2013; 34(1): 15–32.
https://doi.org/10.1177/1071100712460220
18.Malerba F, Milani R, Sartorelli E, Haddo O. Distal oblique first metatarsal osteotomy in grade 3 hallux rigidus: a long-term followup. Foot Ankle Int. 2008; 29(7): 677–82.
https://doi.org/10.3113/FAI.2008.0677
19.Haddad SL. The use of osteotomies in the treatment of hallux limitus and hallux rigidus. Foot Ankle Clin. 2000; 5(3): 629–61.
20.Roukis TS. Clinical outcomes after isolated periarticular osteotomies of the first metatarsal for hallux rigidus: a systematic review. J Foot Ankle Surg. 2010; 49(6): 553–60.
https://doi.org/10.1053/j.jfas.2010.08.014
21.Waizy H, Czardybon MA, Stukenborg-Colsman C, Wingenfeld C, Wellmann M, Windhagen H, et al. Mid- and long-term results of the joint preserving therapy of hallux rigidus. Arch Orthop Trauma Surg. 2010; 130(2): 165–70.
https://doi.org/10.1007/s00402-009-0857-1
22.Canseco K, Long J, Marks R, Khazzam M, Harris G. Quantitative motion analysis in patients with hallux rigidus before and after cheilectomy. J Orthop Res. 2009; 27(1): 128–34.
https://doi.org/10.1002/jor.20711
23.Coughlin MJ, Shurnas PS. Hallux Rigidus: Surgical Techniques (Cheilectomy and Arthrodesis). The Journal of Bone & Joint Surgery. 2004; 86: 119–30.
https://doi.org/10.2106/00004623-200409001-00003

Evaluation of the efficacy of pretreatment chest CT markers in predicting response to neoadjuvant chemoradiotherapy in locally advanced non-small cell lung cancer (NSCLC)

Hüseyin Akkaya[1], Okan Dilek[1], Rukiye Aysu Revanlı Saygılı[1], Ahmet Gülmez[2], Hatice Coşkun[3], Zeynel Abidin Taş[4], Bozkurt Gülek[1]

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

2 Başkent University Hospital, Department of Medical Oncology, Adana, Türkiye

3 University of Health Sciences, Adana City Training and Research Hospital, Department of Radiation Oncology, Adana, Türkiye

4 University of Health Sciences, Adana City Training and Research Hospital, Department of Pathology, Adana, Türkiye

Abstract

Aim: To investigate baseline enhanced chest CT findings that may predict progression or response to neoadjuvant chemoradiotherapy.

Methods: Multiple parameters to be obtained from baseline enhanced chest CT scans of 140 patients with NSCLC who had baseline enhanced chest CT scans before neoadjuvant chemoradiotherapy were noted. In addition to CT features of tumour tissues, age, gender, tumour cell types, lymph node TNM stages, distant metastases on baseline enhanced chest CT, bronchial and vascular invasion were also evaluated. Chest CT findings and changes in tumour tissue at 3 and 6 months during neoadjuvant treatment were noted. Patients were operated after the end of neoadjuvant treatment. It was investigated which parameters could predict response to neoadjuvant treatment and which findings could predict progression.

Results: Progression and mortality rates were found to be low in patients with remission (p<0.001). None of the parameters on baseline chest CT before neoadjuvant treatment predicted response to neoadjuvant treatment. According to the results of the analysis, patients with lymph node station had a 3.69 -fold efect [odds ratio (OR)=3.693, [95% confdence interval (CI)= 1.875–7.274, p=0.041] effect on progression (p<0.001).

Conclusions: It has been observed that any of the parameters that can be obtained from baseline chest CT examination before neoadjuvant treatment are not successful in predicting neoadjuvant treatment response. Lymph node is the only baseline chest CT finding that can predict progression.

Keywords: *Neoadjuvant chemoradiotherapy, non-small cell lung cancer, chest CT, prognosis, pathologic response*

1. Introduction

Lung cancer is the most common cause of cancer-related death worldwide[1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all types of lung cancer, with lung adenocarcinoma and lung squamous cell carcinoma (SCC) accounting for 60% and 15% of histologic subtypes, respectively[1]. With the advent of new developments in neoadjuvant therapy and immunotherapy, the overall survival (OS) of patients with NSCLC has improved significantly. For patients with locally advanced NSCLC, neoadjuvant therapy plays an important role in both staging of lung cancer and providing an opportunity for surgery that effectively improves prognosis[2]. Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection improves survival compared to surgery alone in patients with locally advanced non-small cell lung cancer, especially in patients with a complete pathological response or major pathological response (MPR) (classically defined as a residual tumor burden of <10%)[1]. Neoadjuvant CRT has become a vital strategy to reduce tumor size and facilitate surgical resection[3]. Neoadjuvant CRT also allows interim assessments of response to treatment and prevents the development of micrometastases[4].

Traditional neoadjuvant therapy includes chemotherapy and

Corresponding Author: Hüseyin Akkaya, dr.hsynakkaya@gmail.com, *Received: 30.01.2024, Accepted: 08.03.2024, Available Online Date: 11.03.2024 Cite this article as: Akkaya H, Dilek O, Saygılı RAR, et al. Evaluation of the efficacy of pretreatment chest CT markers in predicting response to neoadjuvant chemoradiotherapy in locally advanced non-small cell lung cancer. J Cukurova Anesth Surg. 2024; 7(1): 32-41. https://doi.org/10.36516/jocass.1427896*

chemoradiation, and revolutionary neoadjuvant therapies for NSCLC are evolving[4]. However, tools and predictive models to estimate the prognosis of patients receiving neoadjuvant therapy followed by lung surgery are still limited[5]. The aim of this study was to evaluate whether chest CT findings can predict neoadjuvant treatment response in patients with locally advanced non-small cell lung cancer.

2. Materials and methods

2.1. Patient Selection and Study Design

This retrospective study was approved by our institutional ethical committee and carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The requirement for informed consent from the patients was waived due to the retrospective nature of the study.

The American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used tool to predict recurrence and survival. For the N descriptor, the lymph node (LN) is based on the lymphatic territory involved without any information on the number of dissected LNs (NDLN) and the number of positive LNs (NPLN). Since January 2017, the 8th edition of TNM in Lung Cancer has been used as the standard for non-small cell lung cancer staging. This staging system was used in our study. In this study, all findings that could be obtained from chest enhanced CT examination of patients with locally advanced lung cancer were included in the investigation. For neoadjuvant treatment response, 3rd and 6th month control chest CT scans were performed and changes around the tumor and changes in tumor size were noted. Tumors in remission and operable tumors were operated. Patients who were not operable after neoadjuvant treatment were excluded from the study (Figure 1).

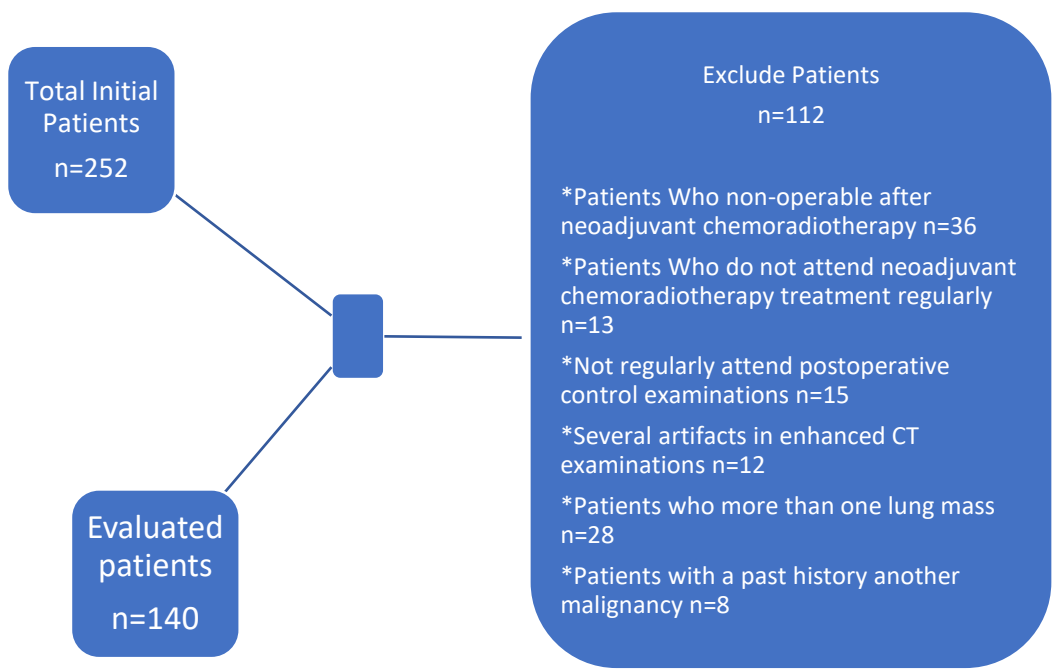
Individuals with diffuse or multiple nodules were excluded. Subsolid, ground glass and cavitary non-solid masses were excluded.

2.2. Chemoradiotherapy Protocols

Although there was previously no standard treatment management in locally advanced lung cancer, treatment algorithms have recently changed with the integration of immunotherapy into neoadjuvant treatment 6. To the best of our previous knowledge, neoadjuvant therapy may improve resectability by decreasing the T stage and nodal disease stage and increasing local regional control by removing residual tumor and nodal disease 7. Data from phase II trials show that neoadjuvant chemoradiotherapy is well tolerated in active patients with good performance status. In contrast, the survival benefit of neoadjuvant chemoradiation compared with induction chemotherapy has not been clearly established due to inconsistent results of Phase III trials.

Figure 1

The initial overall number of patients, together with the number of patients included in the study, is demonstrated. The number of patients excluded from the study and exclusion criteria of the study are shown.



There are 2 different chemotherapies commonly used with concurrent chemoradiotherapy. The first one is the weekly administration of paclitaxel and carboplatin, while the other is the combination of cisplatin and Etoposide. These two chemotherapy combinations have been compared in a previous clinical trial. Although there was no statistical significance in overall survival, there was a numerical improvement in the cisplatin and Etoposide arm. However, this numerical improvement was associated with an increased toxicity profile 8. All of the patients included in this study were patients who received neoadjuvant chemoradiotherapy and then underwent surgery. The combination of carboplatin and paclitaxel is the chemotherapy protocol used simultaneously with radiotherapy in our center because of its easy tolerability. Therefore, weekly carboplatin and paclitaxel treatment was used in all patients in the study. Radiologic response evaluation was performed 4-6 weeks after completion of chemoradiotherapy and operable patients in remission were operated.

Imaging Technique

Thorax CT scans were performed in a 128-detector scanner (Philips Ingenuity 128; Philips, Eindhoven, The Netherlands). All scans were completed in a single breath-hold in the supine position. The standard scanning area was designated as the space between the apex of the lungs and the costophrenic angles. The CT parameters were designated as follows: 80-120 kVp; 100-200 mAs; gantry rotation time = 0.4 s; pitch = 0.8 or 1; slice thickness = 1 mm; and slice reconstruction = 3 mm; FOV :350 mm. Axial, sagittal, and coronal reformatted images were acquired from the raw slices. The radiation dose received by the patients was calculated as 3-5.5 mSv. The enhanced scan was performed using a high-pressure syringe, injecting non-ionic iodine (iohexol; 350 mg/mL; injection amount, 1.5-2 mL/kg; injection rate, 3 mL/s) intravenously through the elbow. The mediastinum window was set [width, 350 Hounsfield units (HU); level, 40 HU], and the lung window was also set (width, 1,200 HU; level, -600 HU). All raters performed their evaluations using separate individual Intellispace Service Healthcare (IPS) workstations.

CT Evaluation

The pathology results of the tumor tissue, presence or absence of additional comorbidities, smoking history, age and gender were completely concealed from the readers. The readers evaluated the localization of the tumor tissue in two ways: central and peripheral. They noted the segments in which the lesion was located and the longest dimension of the lesions. Readers noted the lesion contours under 4 main headings; 1) round smooth 2) macrolobulated 3) microlobulated 4) spiculated. Readers noted the types of calcification of the lesions under 4 headings; 1) no calcification 2) central calcification 3) eccentric calcification 4) coarse calcification. Necrosis status was categorized under 3 headings; 1) no necrosis 2) <50% necrosis 3) >50% necrosis. The types of atelectasis adjacent to the lesion were noted by the readers under 5 headings. 1) no atelectasis 2) subsegmental 3) segmental 4) lobar 5) total atelectasis.

Figure 2

In the mediastinal window of contrast-enhanced thorax CT examination; Coronal (a) and axial (b) section examination shows a mass lesion in the lower lobe of the left lung. Infracarinal lymph node (solid arrow) , pericardial invasion and accompanying pericardial effusion are seen (hollow arrow) (a, b). After neoadjuvant treatment, it was observed that the mass shrank significantly and pericardial invasion and pericardial effusion decreased (c).

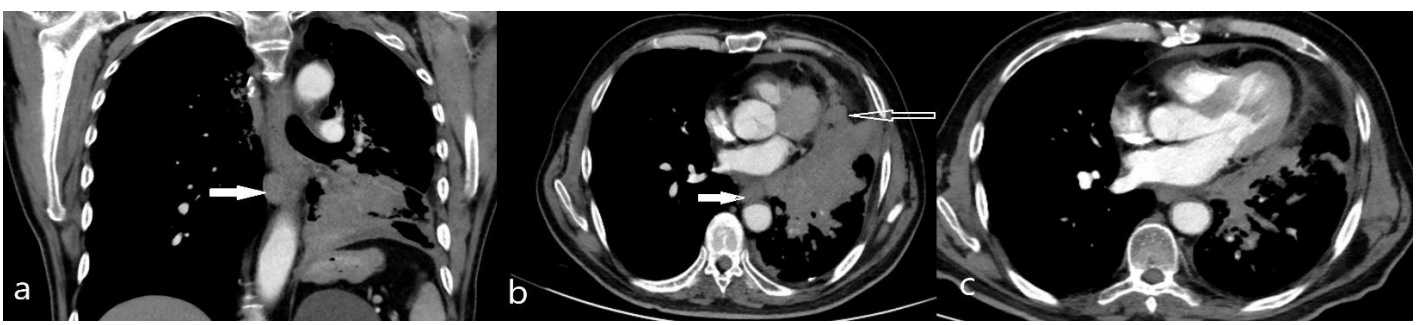
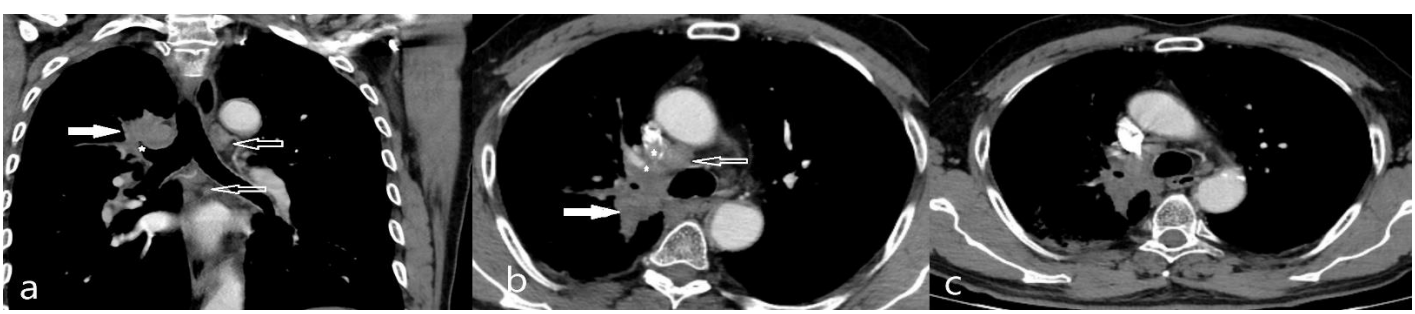


Figure 3

In the mediastinal window of contrast-enhanced thorax CT examination; (a) It is seen that the mass located in the upper lobe (solid arrow) of the right lung infiltrated the posterior bronchus of the right upper lobe (marked with asterisks) and caused thrombus in the superior vena cava and bronchial artery(marked with asterisks), (b). Lymph nodes located at stations 7 and 4L are also seen(hollow arrow). In the thorax CT examination obtained after neoadjuvant treatment; It shows that the thrombus in the superior vena cava has regressed, but there is no change in the size of the mass (c).



parenchymal changes around the tumor tissue were noted by the readers under 7 headings; 1) normal parenchyma 2) ground glass 3) reticular changes (lymphatic) 4) ground glass + reticular changes 5) mosaic attenuation 6) consolidation 7) bronchiectasis. The stage of vascular infiltration of the masses was noted by the readers under 6 headings. 1) absent 2) pulmonary trunk 3) main 4) lobar 5) segmental 6) VCS (Figure 2,3).

The stage at which the masses had respiratory tract infiltration was noted by the readers under 5 headings. 1) no airway infiltration 2) trachea 3) main bronchi 4) intermediate bronchus 5) lobar bronchus (Figure 2,3). The presence or absence of cardiac infiltration of tumor tissue was noted under 4 headings; 1) absent 2) pericardial infiltration 3) infiltration up to myocardium 4) presence of intrachamber thrombus(Figure 2).

Readers noted which lymph node stations had pathologic lymph nodes (lymph nodes with a short axis >10 mm). The presence of distant metastasis on CT scan before neoadjuvant treatment was noted. The presence or absence of pleural effusion in the hemithorax of the lesion was noted (Figure 2,3).

Lung tumours were contoured by three expert readers on the Workstation (Intelli SpacePhilips [IPS], The Netherlands) using a freehand tool to manually segment the lesion. The readers were blinded to the actual histopathologic diagnosis of all cases.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were summarized as mean and standard deviation (median (median) and minimum-maximum where necessary). The Kolmogorov-Smirnov test was used to determine whether the parameters in the study were normally distributed. Mann Whitney U test was used for parameters that did not show normal distribution. Chi-square test was used to compare categorical expressions. Cox Regression test was used to analyze the factors affecting remission and progression. Kaplan Meier test was used in survival analysis. Statistical significance level was taken as 0.05 in all tests.

3. Results

The enhanced chest CT scans, demographic data and number of comorbidities evaluated in the patient groups included in the study are given in Table 1.

Progression and mortality rates were found to be low in patients with remission ($p<0.001$). No significant difference was found between the other parameters in Table 2 ($p>0.05$).

The rate of progression was higher in cases with n2 and n3 in TNM staging ($p<0.001$). The rate of calcification was higher in patients with progression ($p=0.005$) and the rate of pericardial invasion was higher ($p=0.008$). In addition, vascular invasion rate was high in patients who developed progression ($p=0.003$). The mean age of patients with progression was low ($p=0.038$). No significant difference was found between the other parameters in Table 3 ($p>0.05$).

The factors affecting progression were analyzed with Cox regression model in Table 4. Univariate analysis revealed a statistically significant difference between lymph node station, calcification, presence of pericardial invasion, presence of vascular invasion and age variables. In the multivariate cox regression analysis, parameters that were found to be significant in the univariate analysis results were included. According to the results of the analysis, patients with lymph node station 3 had a 3.69 -fold efect [odds ratio (OR)=3.693, [95% confdence interval (CI)= 1.875–7.274, $p=0.041$] effect on progression ($p<0.001$), (Table 4).

Overall survival was 40.1 (months) and progression free survival was 14.8 (months) (Figure 4).

4. Discussion

The aim of this study was to investigate which of the findings on pretreatment chest enhanced CT scan is more successful in predicting histologic response to neoadjuvant therapy in patients with locally advanced NSCLC. Neoadjuvant therapy followed by surgery has recently been applied as a multimodal treatment for locally advanced NSCLC[6]. Accurate patient stratification is becoming increasingly important. Pathological tumor-lymph node-metastasis (pTNM) classification is the most important and routinely applied prognosis prediction tool for malignant disease. MPR or complete pathologic response has been associated with long-term overall survival (OS) in NSCLC patients undergoing neoadjuvant therapy[7,8]. Prognostic information to predict response to treatment in the setting of neoadjuvant therapy can help establish criteria for selecting appropriate surgical candidates [9].

In the study, lymph node stage grouping was performed in patients with lung tumors. It was observed that lymph node stage was not significant in terms of response to neoadjuvant treatment. However, lymph node stage was shown to be effective in progression. Especially in the multivariant analysis, N0 and/or N3 stage group was found to be effective on the progression time. In lung cancer TNM staging 8th edition, N stage varies according to the localisation of lymph nodes. In this study, T stage in TNM staging and lymph node stage and metastasis were investigated separately in terms of both progression and response to treatment. The study showed that N stage was more effective in progression than both T and M stage. In other words, advanced N stage is a poor prognosis in terms of progression independent of TNM staging.

There are many previous studies on whether the contours of lung tumors affect the response to radiotherapy[10]. However, there is no consensus on this issue[8-12]. In our study, tumor contours were not associated with response to neoadjuvant treatment. Similarly, tumor contours were not associated with the time of progression.

There was no significant difference between the subgroups of non-small cell lung tumors in terms of response to neoadjuvant treatment or progression times. These results obtained in our study were consistent with the literature [12,13]. As a matter of fact, lung tumors are divided into two groups as small cell and non-small cell in terms of treatment protocol [8,13].

Localization and infiltrating localization of lung tumors are very important in terms of surgery [14,15]. In the literature, the relationship between postoperative response and localization has been examined [16-18]. In our study, regardless of the areas infiltrated by tumor tissue, the lobe in which the tumor tissue was located, whether it was in a single lobe or extended to more than one lobe, and whether the lesion was centrally or peripherally localized were noted separately. It was observed that the localization of tumor tissue in the lung parenchyma had no effect on neoadjuvant treatment response or progression time.

Recently, the number of studies investigating the relationship between tumor contours in the lung and other localizations and tumor subtypes and grades has increased[19-22]. Tumor contour is one of the most frequently used parameters in tumor analysis, especially in studies performed with artificial intelligence[19,23,24]. It is an accepted fact that spiculated and microlobule lesions suggest malignant tumors [24,25]. In this study, tumor contours were divided into 4 groups by the readers and the relationship between tumor contour and response to neoadjuvant treatment and progression times were examined, but no significant relationship was found.

Table 1

Number of parameters analyzed in the patients included in the study

	Number (n)	Percentage (%)
Gender		
Woman	29	20.7
Male	111	79.3
Cigarette	71	50.7
Emphysema	86	61.4
Comorbidity	120	85.7
DM	9	7.5
HT	6	5.0
History of non-acc malignancy	16	13.3
Previous history of lung disease	31	25.8
Atherosclerotic coronary heart disease	34	28.3
DM and HT	24	20.0
Tissue cell type		
Adenocarcinoma	42	30.0
Squamous HC carcinoma	55	39.3
Neuroendocrine carcinoma	33	23.6
Mucinous adenocarcinoma	10	7.1
Lymph node stage		
0	33	23.6
N1	25	17.9
N2	51	36.4
N3	31	22.1
Baseline CT metastasis	57	40.7
Lung	15	26.3
Brain	9	15.8
Neighbor bone	13	22.8
Distant bone	4	7.0
Surrenal	3	5.3
Lung + brain	3	5.3
Brain + surrenal	3	5.3
Abdomen	5	8.8
Abdomen + surrenal	2	3.5
Lesion localization		
Central	82	58.6
Peripheral	58	41.4
Lobe		
Right upper	50	35.7
Right low	21	15.0
Right middle	7	5.0
Lef upper	51	36.4
Left low	11	7.8
Single lobe		
Single	111	79.3
More than one	29	20.7
Lesion contour		
Round smooth	19	13.6
Lobule	32	22.9
Microlobule	17	12.1
Spiculated	72	51.4
Calcification	66	47.1
Central	15	22.7
Eccentric	26	39.4
Rough	25	37.9
Necrosis		
No necrosis	73	52.1
<%50	39	27.9
>%50	28	20.0
Necrosis 3rd month		
No necrosis	89	63.6
<%50	33	23.6
>%50	18	12.9
Necrosis 6 months		
No necrosis	84	60.0
<%50	32	22.9
>%50	24	17.1
Atelectasis adjacent to the mass	93	66.4
Subsegmental	55	59.1
Segmental	30	32.3
Lobar	6	6.5
Total	2	2.2
Presence of atelectasis on 3rd month Chest CT	99	70.7
Subsegmental	64	64.6
Segmental	23	23.2
Lobar	7	7.1
Total	5	5
Presence of atelectasis on 6th month Chest CT	105	75.0
Subsegmental	51	48.6
Segmental	41	39.0
Lobar	11	10.5
Total	2	1.9
Pleural effusion	37	26.4
Pleural effusion (3rd month Chest CT)	55	39.3
Pleural effusion (6th month Chest CT)	62	44.3
Lung parenchyma adjacent to the lesion		
Normal	11	7.9
Ground glass	8	5.7
Reticular changes (lymphatic)	71	50.7
Ground glass + reticular	25	17.9
Mosaic perfusion	13	9.3
Consolidation	12	8.6
ACC parenchyma adjacent to the lesion (3rd month Chest CT)		
Normal	10	7.1
Ground glass	7	5.0
Reticular changes (lymphatic)	58	41.4
Ground glass + reticular	43	30.7
Mosaic perfusion	6	4.3
Consolidation	16	11.4
ACC parenchyma adjacent to the lesion (6th month Chest CT)		
Normal	15	10.7
Ground glass	7	5.0
Reticular changes (lymphatic)	49	35.0
Ground glass + reticular	47	33.6
Consolidation	8	5.7
Bronchilectasis	14	10.0
Bronchial invasion	89	63.6
Trachea	1	1.1
Main	20	22.5
Intermediate Bronchus	48	43.9
Lobar bronchus	20	22.5
Vascular invasion	84	60.0
Pulmonary trunk	1	1.2
Main	25	29.8
Lobar	28	33.3
Segmental	22	26.2
VCS	8	9.5
Pericardial invasion	57	40.7
Pericardium	48	84.2
Myocardium	6	10.5
Intra-chamber thrombus	3	5.3
Relapse	83	59.3
Progression	72	51.4
Remission		
Yes	99	70.7
Progression without remission	41	29.3
Mortality	59	42.1
	Mean±Ss	**Med (Min-Max)**
Age	63.6±10.1	64 (14-82)
Lesion long size	54.6±23.3	52.5 (14-143)
Average follow-up time	30.7±15.8	28.1 (4.4-68.8)
Progression time	14.8±10.7	12.4 (2.56-50.1)
Mean follow-up time - progression time	15.5±14.3	8.4 (3.9-48.8)

Table 2

Distribution of the analyzed parameters of the patients with and without remission

	No Remission (n=41)	Remission Available (n=99)	p†
	n(%)	n(%)	
Gender			
Woman	11 (26.8)	18 (18.2)	0.251
Male	30 (73.2)	81 (81.8)	
Cigarette	21 (51.2)	50 (50.5)	0.939
Emphysema	26 (63.4)	60 (60.6)	0.756
Comorbidity	34 (82.9)	86 (86.9)	0.544
Tissue cell type			
Adenocarcinoma	13 (31.7)	29 (29.3)	0.636
Squamous HC carcinoma	13 (31.7)	42 (42.4)	
Neuroendocrine carcinoma	12 (29.3)	21 (21.2)	
Mucinous adenocarcinoma	3 (7.3)	7 (7.1)	
Lymph node stage	35 (85.4)	74 (74.7)	0.169
0	6 (14.6)	27 (27.3)	0.405
N1	9 (22)	16 (16.2)	
N2	17 (41.5)	34 (34.3)	
N3	9 (22)	22 (22.2)	
Baseline CT metastasis	17 (41.5)	40 (40.4)	0.908
Lesion localization			
Central	21 (51.2)	61 (61.6)	0.256
Peripheral	20 (48.8)	38 (38.4)	
Lob			
Right upper	17 (41.5)	33 (33.3)	0.701
Right low	4 (9.8)	14 (17.2)	
Right middle	3 (7.3)	4 (4)	
Lef upper	14 (34.2)	37 (37.3)	
Left low	3 (7.3)	8 (8.1)	
Single lobe			
Single	34 (82.9)	77 (77.8)	0.494
More than one	7 (17.1)	22 (22.2)	
Lesion contour			
Round smooth	3 (7.3)	16 (16.2)	0.088
Lobule	6 (14.6)	26 (26.3)	
Microlobule	8 (19.5)	9 (9.1)	
Spiculated	24 (58.5)	48 (48.5)	
Calcification			
Central	8(38)	11(24.4)	0.534
Eccentric	4(19)	16(35.5)	
Rough	9(42.8)	18(40)	
Necrosis			
No	20 (48.8)	53 (53.5)	0.802
<%50	13 (31.7)	26 (26.3)	
>%50	8 (19.5)	20 (20.2)	
Necrosis 3rd month			
No	24 (58.5)	65 (65.7)	0.592
<%50	10 (24.4)	23 (23.2)	
>%50	7 (17.1)	11 (11.1)	
Necrosis 6 months			
No	21 (51.2)	63 (63.6)	0.382
<%50	11 (26.8)	21 (21.2)	
>%50	9 (22)	15 (15.2)	
Atelectasis	31 (75.6)	62 (62.6)	0.139
Atelactasis 3rd month	32 (78)	67 (67.7)	0.220
Atelactasis Month 6	34 (82.9)	71 (71.7)	0.163
Pleural effusion	12 (29.3)	25 (25.3)	0.624
Pleural effusion (3rd month)	19 (46.3)	36 (36.4)	0.271
Pleural effusion (6th month)	21 (51.2)	41 (41.4)	0.288
Lung parenchyma adjacent to the lesion			.
Normal	1 (2.4)	10 (10.1)	0.245
Ground glass	1 (2.4)	7 (7.1)	
Reticular changes (lymphatic)	19 (46.3)	52 (52.5)	
Ground glass + reticular	9 (22)	16 (16.2)	
Mosaic perfusion	6 (14.6)	7 (7.1)	
Consolidation	5 (12.2)	7 (7.1)	
Lung parenchyma adjacent to the lesion 3 months			
Normal	2 (4.9)	8 (8.1)	0.404
Ground glass	-	7 (7.1)	
Reticular changes (lymphatic)	17 (41.5)	41 (41.4)	
Ground glass + reticular	13 (31.7)	30 (30.3)	
Mosaic perfusion	3 (7.3)	3 (3)	
Consolidation	6 (14.6)	10 (10.1)	
Lung parenchyma adjacent to the lesion 6 months			
Normal	5 (12.2)	10 (10.1)	0.095
Ground glass	1 (2.4)	6 (6.1)	
Reticular changes (lymphatic)	9 (22)	40 (40.4)	
Ground glass + reticular	15 (36.6)	32 (32.3)	
Consolidation	3 (7.3)	5 (5.1)	
Bronchiectasis	8 (19.5)	6 (6.1)	
Bronchial invasion	27 (65.9)	62 (62.6)	0.718
Vascular invasion	25 (61)	59 (59.6)	0.879
Pericardial invasion	16 (39)	41 (41.4)	0.793
Progression	36 (87.8)	51 (51.5)	**<0.001****
Mortality	28 (68.3)	31 (31.3)	**<0.001****
	Mean±Ss	**Mean±Ss**	**p‡**
Age	63.7±9.3	63.6±10.5	0.865
Size of the lesion long axis	57.5±25.3	53.5±22.5	0.558

DM: diabetes mellitus, HT: hypertension, VCS: vena cava superior

Table 3

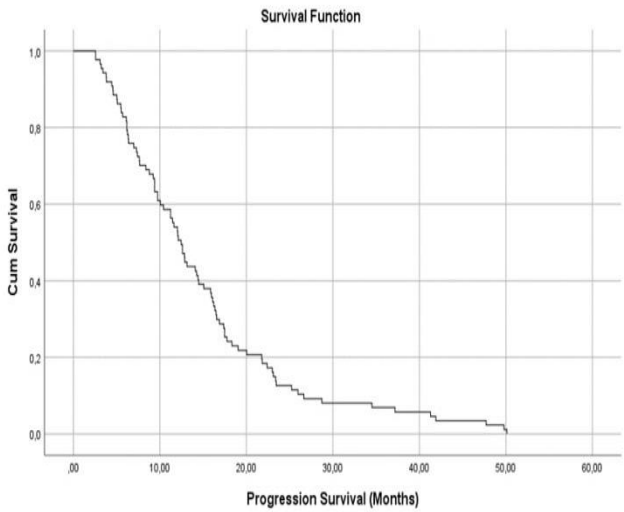
Distribution of analyzed parameters of progressing and non-progressing patients

	No Progression (n=53)	Progression Available (n=87)	p†
	n(%)	n(%)	
Gender			
Woman	10 (18.9)	19 (21.8)	0.674
Male	43 (81.1)	68 (78.2)	
Cigarette	26 (49.1)	45 (51.7)	0.759
Emphysema	30 (56.6)	56 (64.4)	0.360
Comorbidity	48 (90.6)	72 (82.8)	0.200
Tissue cell type			
Adenocarcinoma	17 (32.1)	25 (28.7)	0.670
Squamous HC carcinoma	23 (43.4)	32 (36.8)	
Neuroendocrine carcinoma	10 (18.9)	23 (26.4)	
Mucinous adenocarcinoma 3	3 (5.7)	7 (8)	
Lymph node stage	37 (69.8)	72 (82.8)	0.074
0	17 (32.1)	16 (18.4)	**<0.001****
N1	13 (24.5)	12 (13.8)	
N2	21 (39.6)	30 (34.5)	
N3	2 (3.8)	29 (33.3)	
Baseline CT metastasis	17 (32.1)	40 (46.0)	0.104
Lesion localization			
Central	33 (62.3)	49 (56.3)	0.489
Peripheral	20 (37.7)	38 (43.7)	
Lob			
Right upper	13 (24.5)	37 (42.5)	0.357
Right low	11 (20.8)	10 (12.5)	
Right middle	3 (5.7)	4 (4.6)	
Lef upper	24 (45.3)	27 (30.9)	
Left low	2 (3.8)	9 (10.3)	
Single lobe			
Single	40 (75.5)	71 (81.6)	0.385
More than one	13 (24.5)	16 (18.4)	
Lesion contour			
Round smooth	9 (17)	10 (11.5)	0.757
Lobule	13 (24.5)	19 (21.8)	
Microlobule	6 (11.3)	11 (12.6)	
Spiculated	25 (47.2)	47 (54)	
Calcification			
Central	10(18.8)	9(10.3)	**0.005****
Eccentric	2(3.7)	32(36.7)	
Rough	5(9.4)	8(9.1)	
Necrosis			
No	29 (54.7)	44 (50.6)	0.778
<%50	15 (28.3)	24 (27.6)	
>%50	9 (17)	19 (21.8)	
Necrosis 3rd month			
No	30 (56.6)	59 (67.8)	0.355
<%50	14 (26.4)	19 (21.8)	
>%50	9 (17)	9 (10.2)	
Necrosis 6 months			
No	29 (54.7)	55 (63.2)	0.072
<%50	10 (18.9)	22 (25.3)	
>%50	14 (26.4)	10 (11.5)	
Atelectasis	33 (62.3)	60 (69)	0.415
Atelectasis 3rd month	36 (67.9)	63 (72.4)	0.571
Atelectasis Month 6	39 (73.6)	66 (75.9)	0.763
Thickening of pleural effusion	18 (34)	19 (21.8)	0.115
Pleural effusion (3rd month)	22 (41.5)	33 (37.9)	0.674
Pleural effusion (6th month)	23 (43.4)	39 (44.8)	0.869
Lung parenchyma adjacent to the lesion			
Normal	6 (11.3)	5 (5.7)	0.381
Ground glass	2 (3.8)	6 (6.9)	
Reticular changes (lymphatic)	26 (49.1)	45 (51.7)	
Ground glass + reticular	12 (22.6)	13 (14.9)	
Mosaic perfusion	5 (9.4)	8 (9.2)	
Consolidation	2 (3.8)	10 (11.5)	
Lung parenchyma adjacent to the lesion 3 months			
Normal	3 (5.7)	7 (8)	0.728
Ground glass	2 (3.8)	5 (5.7)	
Reticular changes (lymphatic)	19 (35.8)	39 (44.8)	
Ground glass + reticular	20 (37.7)	23 (26.4)	
Mosaic perfusion	2 (3.8)	4 (4.6)	
Consolidation	7 (13.2)	9 (10.3)	
Lung parenchyma adjacent to the lesion 6 months			
Normal	6 (11.3)	9 (10.3)	0.387
Ground glass	2 (3.8)	5 (5.7)	
Reticular changes (lymphatic)	22 (41.5)	27 (31)	
Ground glass + reticular	19 (35.8)	28 (32.2)	
Consolidation	1 (1.9)	7 (8)	
Bronchilectasis	3 (5.7)	11 (12.6)	
Bronchial invasion	33 (62.3)	56 (64.4)	0.802
Vascular invasion	29 (54.7)	55 (63.2)	**0.003****
Pericardial invasion	29 (54.7)	28 (32.2)	**0.008***
Mortality	17 (32.0)	42 (48.2)	**<0.001****
	Mean±Ss	**Mean±Ss**	**p‡**
Age	64.9±12.1	62.8±8.7	**0.038***
Lesion long axis dimension	54.6±24.4	54.6±22.8	0.899

*DM: diabetes mellitus, HT: hypertension, VCS: vena cava superior, *p<0.05, **p<0.01, †: Chi-square, ‡: Mann Whitney U*

Figure 4

Graph of progression free survival and overall survival times of patients.



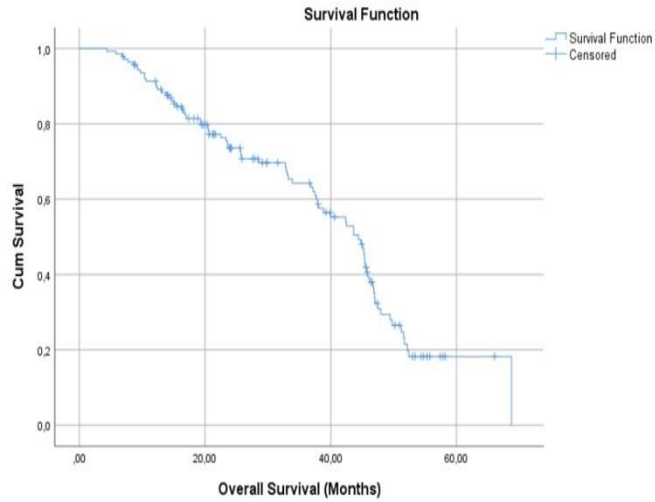


Table 4

Cox regression model of factors affecting progression

	p	Exp(B)	95% CI	
			Lower	Upper
Lymph node station				
0	**0.001****			
N1	0.406	1.388	0.640	3.009
N2	0.058	1.862	0.978	3.542
N3	**<0.001****	3.693	1.875	7.274
Presence of calcification	0.207	1.333	0.853	2.083
Vascular invasion	**0.003****	1.473	1.125	3.652
Presence of pericardial invasion	0.324	0.783	0.482	1.272
Age	0.079	1.024	0.997	1.052

***p<0.01, Cox regression*

Necrosis and cavity are not uncommon findings in lung tumors [9,26]. Lesions with cavities were not included in the study. The presence of necrosis (0, <50%, >50%) on the baseline enhanced CT scan before neoadjuvant treatment was analyzed by the readers. In addition, necrosis rates at the 3rd and 6th month of the treatment follow-up were noted. The presence or absence of necrosis before treatment or necrosis developing during treatment was not associated with neoadjuvant treatment response or time to progression.

Calcification is not uncommon in both benign and malignant lung tumors [27,28]. While eccentric calcification is more common in malignant lesions, coarse and central calcification is more common in benign lesions[29-31]. Our aim in this study was to evaluate whether calcification can predict response to treatment or progression. In the study, there was no significant difference in response to neoadjuvant treatment in cases with and without calcification , but progression was more common in cases with calcification (especially eccentric calcification).

We examined whether the presence of atelectasis in the neighborhood of the mass was associated with response to neoadjuvant treatment. Atelectasis was classified as 4 types by the readers. Both the baseline enhanced CT scan at the time of diagnosis and the presence of atelectasis at 3 and 6 months during treatment follow-up were noted. However, atelectasis both at baseline enhanced CT scan and during treatment was not associated with neoadjuvant treatment response or time to progression.

The presence of pleural effusion in the hemithorax with tumor tissue was examined both at baseline enhanced chest CT examination and at 3 and 6 months during the treatment period. However, pleural effusion at any period was not associated with neoadjuvant treatment response or time to progression.

Density changes other than atelectasis around the tumor tissue were examined both at baseline enhanced chest CT examination and at 3 and 6 months during the treatment period. However, peritumoral density changes in any period were not correlated with neoadjuvant treatment response or time to progression.

There was no significant difference in response to neoadjuvant treatment in patients with bronchial invasion, vascular invasion and pericardial invasion compared to patients without these invasions. However, progression was observed earlier in patients with bronchial, vascular and pericardial invasion compared to those without. Especially vascular invasion had a greater effect on progression compared to the others. It is not surprising that progression is seen earlier in cases with vascular invasion. The ease of spread of micrometastases and/or tumour cells via haematogenous route especially in cases with vascular invasion is already known in other tumours[1,8,13]. We think that the fact that the lymph node stage is another effective factor in the progression of lung tumours supports this idea.

Previous studies have shown that neoadjuvant treatment has a positive effect on both progression free survival and overall survival[2,8,27]. In this study, both progression times were longer and mortality was lower in patients in remission.

Limitations

Our study has some limitations. The main ones are; 1) Using artificial intelligence and obtaining quantitative data, especially in the evaluation of tumor heterogeneity and tumor contours, would have made our study much more valuable. 2) The fact that metabolic tumor volume (MTV) was not evaluated from PET CT examinations before neoadjuvant treatment can be considered one of the limitations of our study. However, due to the retrospective nature of the study, most of the patients did not have a PET CT scan after neoadjuvant treatment. 3) Since the study was not interobserver, the concordance of the chest CT findings between the readers and their usability in routine clinical practice could not be examined.

5. Conclusion

None of the findings on chest CT examination before neoadjuvant therapy have been shown to be successful in predicting response to neoadjuvant therapy. The findings that can predict progression on a baseline chest CT scan are vascular invasion, lymph node staging and pericardial invasion. Vascular invasion, lymph node stage advanced cases, pericardial invasion and calcification during baseline chest CT scan are findings that can predict progression. Lymph node is the most valuable of these in predicting progression.

Statement of ethics

The ethical approval was provided by the Clinical Research Ethics Committee of the Adana City Training and Research Hospital on 2023, with decision number 2767.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

1. substantial contributions to conception and design, acquisition of data: Hüseyin Akkaya, Okan Dilek, Bozkurt Gülek, Rukiye Aysu Revanlı Saygılı, Hatice Coşkun, Zeynel Abidin Taş

2. revising it critically for important intellectual content: Hüseyin Akkaya , Okan Dilek , Bozkurt Gülek,Ahmet Gülmez

3. final approval of the version to be published , analysis: Hüseyin Akkaya , Okan Dilek , Bozkurt Gülek, Ahmet Gülmez, Hatice Coşkun

4. agree to be accountable for all aspects of the work if questions : Hüseyin Akkaya , Okan Dilek , Bozkurt Gülek, Rukiye Aysu Revanlı Saygılı, Zeynel Abidin Taş

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
https://doi.org/10.3322/caac.21654
2. Wang Q, Wang S, Sun Z, Cao M, Zhao X. Evaluation of log odds of positive lymph nodes in predicting the survival of patients with non-small cell lung cancer treated with neoadjuvant therapy and surgery: a SEER cohort-based study. BMC Cancer. 2022;22:801.
https://doi.org/10.1186/s12885-022-09908-3
3. Shen J, Sun N, Zens P et al. Spatial metabolomics for evaluating response to neoadjuvant therapy in non-small cell lung cancer patients. Cancer Commun (Lond). 2022;42:517-535.
https://doi.org/10.1002/cac2.12310
4. Saw SPL, Ong BH, Chua KLM et al. Revisiting neoadjuvant therapy in non-small-cell lung cancer. Lancet Oncol. 2021;22:e501-e516.
https://doi.org/10.1016/S1470-2045(21)00383-1
5. Rosner S, Liu C, Forde PM et al. Association of Pathologic Complete Response and Long-Term Survival Outcomes Among Patients Treated with Neoadjuvant Chemotherapy or Chemoradiotherapy for NSCLC: A Meta-Analysis. JTO Clin Res Rep. 2022 Jul 31;3(9):100384.
https://doi.org/10.1016/j.jtocrr.2022.100384
6. Godoy LA, Chen J, Ma W P et al. Emerging precision neoadjuvant systemic therapy for patients with resectable non-small cell lung cancer: current status and perspectives. Biomark Res 2023;11:7.
https://doi.org/10.1186/s40364-022-00444-7
7. Blumenthal GM, Bunn PA Jr, Chaft JE et al. Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer. J Thorac Oncol 2018;13:1818-31.
https://doi.org/10.1016/j.jtho.2018.09.017
8. Liang J, Bi N, Wu S et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017;28):777-783.
https://doi.org/10.1093/annonc/mdx009
9. Cheng Y, Chen ZY, Huang JJ et al. Efficacy evaluation of neoadjuvant immunotherapy plus chemotherapy for non-small-cell lung cancer: comparison of PET/CT with postoperative pathology. Eur Radiol. 2023;33:6625-6635.
https://doi.org/10.1007/s00330-023-09922-4
10. Khorrami M, Jain P, Bera K et al. Predicting pathologic response to neoadjuvant chemoradiation in resectable stage III non-small cell lung cancer patients using computed tomography radiomic features. Lung Cancer. 2019;135:1-9.
https://doi.org/10.1016/j.lungcan.2019.06.020
11. Yue D, Liu W, Chen C et al. Circulating tumor DNA predicts neoadjuvant immunotherapy efficacy and recurrence-free survival in surgical non-small cell lung cancer patients. Transl Lung Cancer Res. 2022;11:263-276.
https://doi.org/10.21037/tlcr-22-106
12. Bao Y, Gu C, Xie H et al. Comprehensive study of neoadjuvant targeted therapy for resectable non-small cell lung cancer. Ann Transl Med. 2021;9:493.
https://doi.org/10.21037/atm-21-1134
13. Tanahashi M, Suzuki E, Yoshii N et al. Role of fluorodeoxyglucose-positron emission tomography in predicting the pathological response and prognosis after neoadjuvant chemoradiotherapy for locally advanced non-small-cell lung cancer. Interact Cardiovasc Thorac Surg. 2022;35:113.
https://doi.org/10.1093/icvts/ivac113
14. Zhang J, Zhao X, Zhao Y et al. Value of pre-therapy 18F-FDG PET/CT radiomics in predicting EGFR mutation status in patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging. 2020;47:1137-1146.
https://doi.org/10.1007/s00259-019-04592-1
15. Chetan MR, Gleeson FV. Radiomics in predicting treatment response in non-small-cell lung cancer: current status, challenges and future perspectives. Eur Radiol. 2021;31:1049-1058.
https://doi.org/10.1007/s00330-020-07141-9
16. Dissaux G, Visvikis D, Da-Ano R et al. Pretreatment 18F-FDG PET/CT Radiomics Predict Local Recurrence in Patients Treated with Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: A Multicentric Study. J Nucl Med. 2020;61:814-820.
https://doi.org/10.2967/jnumed.119.228106
17. Nestle U, Schimek-Jasch T, Kremp S et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomized, controlled trial. Lancet Oncol. 2020;21:581-592.
https://doi.org/10.1016/S1470-2045(20)30013-9
18. Khorrami M, Prasanna P, Gupta A, Patil P et al. Changes in CT Radiomic Features Associated with Lymphocyte Distribution Predict Overall Survival and Response to Immunotherapy in Non-Small Cell Lung Cancer. Cancer Immunol Res. 2020;8:108-119.
https://doi.org/10.1158/2326-6066.CIR-19-0476
19. Bortolotto C, Lancia A, Stelitano C et al. Radiomics features as predictive and prognostic biomarkers in NSCLC. Expert Rev Anticancer Ther. 2021;21:257-266.
https://doi.org/10.1080/14737140.2021.1852935
20. Liberini V, Mariniello A, Righi L et al. NSCLC Biomarkers to Predict Response to Immunotherapy with Checkpoint Inhibitors (ICI): From the Cells to In Vivo Images. Cancers (Basel). 2021;13:4543.

https://doi.org/10.3390/cancers13184543
21. Seban RD, Mezquita L, Berenbaum A et al. Baseline metabolic tumor burden on FDG PET/CT scans predicts outcome in advanced NSCLC patients treated with immune checkpoint inhibitors. Eur J Nucl Med Mol Imaging. 2020;47:1147-1157.
https://doi.org/10.1007/s00259-019-04615-x
22. Rosner S, Liu C, Forde PM et al. Association of Pathologic Complete Response and Long-Term Survival Outcomes Among Patients Treated With Neoadjuvant Chemotherapy or Chemoradiotherapy for NSCLC: A Meta-Analysis. JTO Clin Res Rep. 2022;3:100384.
https://doi.org/10.1016/j.jtocrr.2022.100384
23. Zarogoulidis P, Matthaios D, Kosmidis C et al. Effective early diagnosis for NSCLC: an algorithm. Expert Rev Respir Med. 2021;15:1437-1445.
https://doi.org/10.1080/17476348.2021.1969916
24. Han Y, Ma Y, Wu Z et al. Histologic subtype classification of non-small cell lung cancer using PET/CT images. Eur J Nucl Med Mol Imaging. 2021;48:350-360.
https://doi.org/10.1007/s00259-020-04771-5
25. Koyasu S, Nishio M, Isoda H et al. Usefulness of gradient tree boosting for predicting histological subtype and EGFR mutation status of non-small cell lung cancer on 18F FDG-PET/CT. Ann Nucl Med. 2020;34:49-57.
https://doi.org/10.1007/s12149-019-01414-0
26. Dissaux G, Visvikis D, Da-Ano R et al. Pretreatment 18F-FDG PET/CT Radiomics Predict Local Recurrence in Patients Treated with Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer: A Multicentric Study. J Nucl Med. 2020;61:814-820.
https://doi.org/10.2967/jnumed.119.228106
27. Leader AM, Grout JA, Maier BB et al. Single-cell analysis of human non-small cell lung cancer lesions refines tumor classification and patient stratification. Cancer Cell. 2021;39:1594-1609.
https://doi.org/10.1016/j.ccell.2021.10.009
28. Kan CFK, Unis GD, Li LZ et al. Circulating Biomarkers for Early Stage Non-Small Cell Lung Carcinoma Detection: Supplementation to Low-Dose Computed Tomography. Front Oncol. 2021;11:555331.
https://doi.org/10.3389/fonc.2021.555331
29. Hattori A, Suzuki K, Takamochi K et al. Japan Clinical Oncology Group Lung Cancer Surgical Study Group. Prognostic impact of a ground-glass opacity component in clinical stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg. 2021;161:1469-1480.
https://doi.org/10.1016/j.jtcvs.2020.01.107
30. Akinci D'Antonoli T, Farchione A, Lenkowicz J et al. CT Radiomics Signature of Tumor and Peritumoral Lung Parenchyma to Predict Nonsmall Cell Lung Cancer Postsurgical Recurrence Risk. Acad Radiol. 2020;27:497-507.
https://doi.org/10.1016/j.acra.2019.05.019
31. Nakanishi Y, Masuda T, Yamaguchi K et al. Pre-existing interstitial lung abnormalities are risk factors for immune checkpoint inhibitor-induced interstitial lung disease in non-small cell lung cancer. Respir Investig. 2019;57:451-459.
https://doi.org/10.1016/j.resinv.2019.05.002

COVID-19 Vaccination Rate in Patients Admitted to The Immunology and Allergy Outpatient Clinic

Merve Erkoç [1], Selver Seda Mersin [1]

1 Division of Immunology and Allergy, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye

Abstract

Aim: Misinformation, lack of awareness, and beliefs about vaccines can cause hesitations about vaccines and affect the rate of vaccination. We aimed to reveal the vaccination rates against coronavirus disease-19 (COVID-19) (vaccine types and dose), and the reasons for not being vaccinated in patients admitted to the immunology and allergy outpatient clinic. In addition, we aimed to find out whether allergic reactions were observed in vaccinated patients.

Methods: The history of COVID-19 and vaccination of patients admitted to the Immunology and Allergy Outpatient Clinic between December 2021 and February 2022 were evaluated retrospectively.

Results: In our study, which included 451 patients, the median age of the patients was 35 (range 18-82), and 61.2% were women. 16.9% of the patients admitted to the immunology and allergy outpatient clinic were never vaccinated, while the rate of those who did not receive two doses of vaccine was 26.6%. The top three reasons for not being vaccinated were fear of allergies, fear of adverse effects, and distrust of the vaccine, respectively. Unvaccinated patients were younger, which is statistically significant. Vaccination rate was found to be lower in drug allergy and immunodeficiencies compared to other disease groups.

Conclusions: Understanding the causes of vaccine hesitations and increasing the vaccination rate by organizing public health campaigns is an important point in the control of the pandemic. Despite being rare, allergic reactions can be observed with COVID-19 vaccines. Therefore, immunologists and allergists play an important role in the COVID-19 vaccine program.

Keywords: *Coronavirus disease-19, vaccination, hesitancy, allergic reaction*

1. Introduction

Vaccines against coronavirus disease-19 (COVID-19) are important to control the current pandemic. Side effects from the protective immune response of the vaccine are not considered an allergic reaction, and vaccines often cause side effects. Vaccines against COVID-19 are new and some have been created using a novel mechanism of action. Therefore, vaccines created with this new mechanism may have a higher risk of allergic reaction compared to conventional vaccines [1]. An extremely low rate of anaphylaxis is observed against COVID-19 vaccines. But public concern about adverse effects, including allergic reactions, still causes vaccine hesitancy [2]. Polyethylene glycol (PEG) is thought to be the most likely culprit for an allergic reaction, and report of anaphylaxis against PEG-containing messenger RNA (mRNA) vaccines raise public concern and increase vaccine hesitancy [3].

Corresponding Author: Merve Erkoç, drmerverkoc@gmail.com, Received: 02.02.2024, Accepted: 06.03.2024, Available Online Date: 11.03.2024 Cite this article as: Erkoç M, Mersin SS. COVID-19 Vaccination Rate in Patients Admitted to The Immunology and Allergy Outpatient Clinic. J Cukurova Anesth Surg. 2024; 7(1): 42-6. https://doi.org/10.36516/jocass.1429524

Pre-vaccine allergy assessment is recommended for individuals with a history of anaphylaxis to an injectable drug or vaccine containing PEG or its derivatives, anaphylaxis to oral/topical PEG-containing products, recurrent anaphylaxis of unknown cause, suspected or confirmed allergy to any mRNA vaccine, and confirmed allergy to PEG or its derivatives [4]. Misinformation, lack of awareness and beliefs about vaccines can cause hesitations about vaccines. It is important to identify the population experiencing COVID-19 vaccine hesitancy and to reveal the reasons for hesitation in this population. In this way, vaccination hesitancy can be combated by organizing public health campaigns [5].

We aimed to reveal the rate of vaccination against COVID-19 of patients who admitted to the immunology and allergy outpatient clinic with various complaints, which vaccine and how many doses, and the reasons for not being vaccinated in patients who were not vaccinated. We wanted to have an idea about what we can do to support vaccine acceptance as an immunologist/allergist by revealing the reasons. In addition, we wondered whether allergic reactions were observed in patients who were vaccinated.

2. Materials and methods

2.1. Study design

In our retrospective study, patients who admitted to Immunology and Allergy Outpatient Clinic between December 2021 and February 2022 with various complaints were included. The study protocol was approved by the local Ethics Committee.

A data form including age, gender, employment status, marital status, comorbidities, smoking history, admission complaints and allergic diseases of the patients was created. We also added their COVID-19 history, whether they were vaccinated, if they were vaccinated, which vaccine, how many doses, and if they weren't vaccinated, the reasons for not getting vaccinated. Finally, we added the histories of allergic reactions to the vaccine. Demographic characteristics of the patients, information about COVID-19 and vaccination against COVID-19 were obtained from the medical records of the patients at their outpatient clinic applications.

2.2. Statistics analysis

All statistical analyzes were performed using the SPSS software package for Windows 11.5 (SPSS Inc., Chicago, IL, USA). The median (minimum – maximum) for the non-normally distributed variables, and the number of persons (n) and (%) for the nominal variables will be shown. In order to compare independent groups in terms of categorical variables, chi-square test, that of metric variables, Mann-Whitney U test were done. Statistical significance score was given as 0.05.

3. Results

In our study, which included 451 patients, the median age of the patients was 35 (range18-82), and 61.2% were women. 67% of the patients were married and 41.2% were working. 14.2% of the patients had comorbidity and 23.1% were smokers. 67.8% of the patients have immunology and allergic diseases. Considering the reasons for admission to the immunology and allergy clinic, the first three reasons were rhinitis symptom, urticaria and/or angioedema, and drug allergy, respectively. The demographic characteristics of the patients are shown in Table-1.

Thirty-point four percent of the patients were diagnosed with COVID-19, and the information of two people is not available. While the rate of single dose COVID-19 vaccine of the patients who admitted to our immunology and allergy diseases outpatient clinic was 83.1%, the rate of patients who received at least two doses of vaccine was 73.4%. The highest rate among vaccinated patients was in patients vaccinated with 2 doses of m-RNA vaccine with a rate of 46.9%. This was followed by those vaccinated with 3 doses of m-RNA vaccine at the rate of 16.8% and those vaccinated with two doses of inactivated vaccine at the rate of 9.3%. The COVID-19 diagnosis rate and COVID-19 vaccination characteristics of the patients are given in Table-2.

The rate of those who were not vaccinated even one dose was 21.5% in the 18-40 age group, 9.3% in the 41-64 age group, and 0% in the 65 and older age group. The patients who were not vaccinated were younger. The median age of the unvaccinated patients was 29 (range 18-64) while the median age of the vaccinated patients was 36 (range 18-82) ($p<0.001$).

In the subgroups of immunology and allergy diseases, the rate of vaccination with at least two doses was highest in allergic rhinitis with 84.4% and the lowest in immunodeficiencies with 25%. 84.4% of those with allergic rhinitis were vaccinated at least 2 doses, and this rate was significantly higher than those without rhinitis ($p<0.001$). The vaccination rate in the immunology and allergy diseases subgroup is given in Table 3.

Table 1

Demographic characteristics of patients

Age (year) median (min-max)	35 (18-82)
Gender n (%)	
Female	276 (61.2)
Male	175 (38.8)
Marital status n (%)	
Single	149 (33)
Married	302 (67)
Employment status n (%)	
Is studying	35 (7.8)
Not working	230 (51)
Working	186 (41.2)
Comorbidity n (%)	
No	387 (85.8)
Yes	64 (14.2)
Smoking n (%)	
No	347 (76.9)
Yes	104 (23.1)
Presenting symptoms n (%)	
Pruritus	46 (10.2)
Urticaria and/or angioedema	79 (17.5)
Dermatitis	7 (1.6)
Rhinitis	162 (35.9)
Cough	27 (6)
Asthma	26 (5.8)
Drug allergy	74 (16.4)
Immunodeficiency	8 (1.8)
Food allergy	3 (0.7)
Others	19 (4.2)
Immunology and Allergic Disease n (%)	
No	145 (32.2)
Yes	306 (67.8)

Table 2

The COVID-19 diagnosis rate and COVID-19 vaccination characteristics of the patients

COVID-19 n (%)	
Yes	137 (30.4)
No	311 (69)
Unknown	2 (0.7)
At least one dose of vaccine against COVID-19 n (%)	
Yes	375 (83.1)
No	76 (16.9)
At least two doses of vaccine against COVID-19 n (%)	
Yes	331 (73.4)
No	120 (26.6)
Vaccination subgroups (n=375) n (%)	
1 dose of inactived	10 (2.7)
1 dose of m-RNA	34 (9.1)
2 doses of inactived	35 (9.3)
2 doses of m-RNA	176 (46.9)
3 doses of inactived	18 (4.8)
3 doses of m-RNA	63 (16.8)
2 doses of inactived, 1 dose of m-RNA	23 (6.1)
1 dose of inactived, 2 doses of m-RNA	1 (0.3)
4 doses of inactived	1 (0.3)
2 doses of inactived, 2 doses of m-RNA	13 (3.5)
2 doses of inactived, 3 doses of m-RNA	1 (0.3)

COVID-19: Coronavirus disease-19, m-RNA: messenger RNA

Forty-four patients (9.7%) did not receive the second dose of the vaccine and the reason was fear of adverse effects in 27% of all patients and was unknown in 30% of the patients. Other reasons for not getting the second dose were; not having the opportunity to be vaccinated, not needing to be vaccinated and fear of an allergic reaction, respectively. The reasons for not getting the second dose are shown in Figure 1.

It was not known why 14% of the patients were never vaccinated. The most common reasons for not getting the vaccine were fear of allergies and advers effects, distrust of the vaccine, being in the pregnancy-breastfeeding period, waiting for the Turkish vaccine, not considering the vaccine as a necessity. The reasons for patients who have never been vaccinated are shown in Figure 2.

Ten patients described an allergic reaction to the COVID-19 vaccine, 80% of whom were women. 80% of these patients had an allergic disease and 40% had a history of drug allergy. 80% of the patients had a reaction with the m-RNA vaccine. There were urticaria and/or angioedema in seven patients, delayed urticaria in one patient, and anaphylaxis in two patients. Two patients with anaphylaxis had received m-RNA vaccine.

Table 3

Vaccination rate in Immunology and Allergy Diseases subgroups

Immunology and Allergy diseases (n=306) n (%)	
No	45 (14.7)
Single dose	35 (11.4)
At least two doses	226 (73.9)
Asthma (n=59) n (%)	
No	8 (13.6)
Single dose	3 (5.1)
At least two doses	48 (81.4)
Allergic rhinitis (n=147) n (%)	
No	12 (8.2)
Single dose	11 (7.5)
At least two doses	124 (84.4)
Drug allergy (n=109) n (%)	
No	25 (22.9)
Single dose	11 (10.1)
At least two doses	73 (67)
Immunodeficiency (n=8) n (%)	
No	3 (37.5)
Single dose	3 (37.5)
At least two doses	2 (25)
Urticaria and/or angioedema (n=73) n (%)	
No	11 (15.1)
Single dose	12 (16.4)
At least two doses	50 (68.5)
Food allergy (n=5) n (%)	
No	0 (0)
Single dose	1 (20)
At least two doses	4 (80)

Figure 1

Reasons for not having a 2nd dose

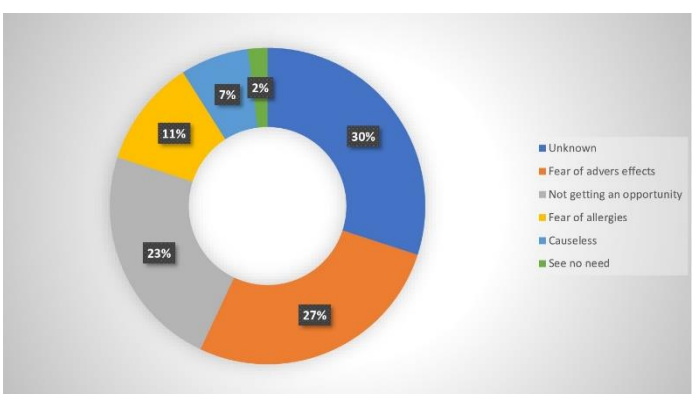
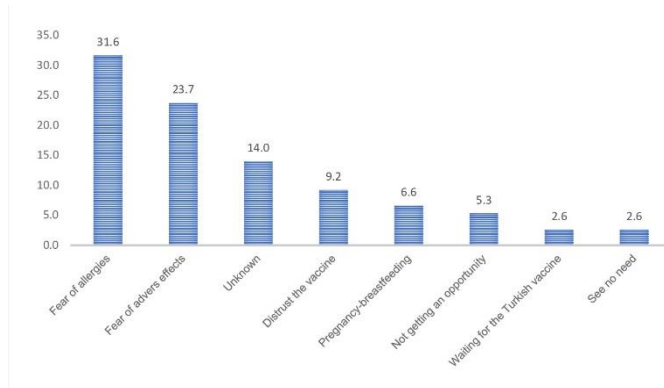


Figure 2

Reasons for not having a 2nd dose



4. Discussion

Here we present the COVID-19 vaccination rate of 451 patients who admitted to our immunology and allergy outpatient clinic. We assessed the patients characteristics, which vaccines and how many doses they received, the reasons why they were not vaccinated and whether there was an allergic reaction with the vaccine.

The proportion of unvaccinated people who dislike and completely reject vaccines is approximately 14% worldwide [6]. In the study conducted in Turkey with 384 people in December 2020, 45.3% of the participants were hesitant about getting the COVID-19 vaccine approved by the Ministry of Health [7]. In another study, 31% of respondents in Turkey and 14% in the UK were unsure about getting a COVID-19 vaccine, while 3% of respondents in both countries refused to be vaccinated [8]. In Singapore, 98.9% of primary care healthcare workers were fully vaccinated and 73.8% of eligible healthcare workers taken the booster. Among healthcare workers, less hesitation was observed with booster compared to the first dose [9]. The pooled rate of COVID-19 vaccine acceptance in Ethiopia was found to be 56.02% [10]. In the study, which included low- and low-middle-income countries, the pooled effect size of the COVID-19 vaccine acceptance rate was 58.5% and the pooled vaccine hesitancy rate was 38.2%. The predictor of willingness to accept the vaccine was found to be male and perceiving the risk of COVID-19 infection [11]. In a survey conducted in Romania, 39.2% of the participants stated that they were vaccinated, 25.6% wanted to be vaccinated, 29.5% were against vaccination. The most important reason for vaccine rejection was that the vaccine was not safe enough and there was a risk of serious side effects [12]. In our study, the rate of people who could not be vaccinated was 16.9%. People's awareness and availability of vaccines may vary from country to country and may differ in various populations and times.

In a study of adults, the intention to vaccinate increased from 67.6% in November 2020 to 84.8% in May 2021. Individuals aged 65 and over were more willing to be vaccinated, but the differences between age groups decreased over time [13]. In a study conducted in Italy in young adults aged 18-40, vaccine hesitancy/resistance was observed as 25% [14]. In a study of adults aged 18-29 years, the intention to accept the vaccine was 84.3% and 59.7% in Canada and France, respectively [15]. In our study, the rate of not being vaccinated was quite high in the 18-40 age range compared to those over 40 years old. All people over the age of 65 were vaccinated. Unvaccinated patients were younger, which is statistically significant.

In our study, the highest rate of vaccination was observed in patients with food allergy, allergic rhinitis and asthma. The rate of vaccination of at least two doses in the allergic rhinitis group was

significantly higher than those without allergic rhinitis. Vaccination rate was found to be lower in drug allergy and immunodeficiencies compared to other disease groups. Especially in immunodeficiencies, the rate of vaccination with at least two doses is 25% and it is the group with the lowest rate. However, patients with immunodeficiencies are at risk of chronic COVID-19 due to inadequate immune response. This may lead to the rapid emergence of vaccine-resistant mutants and high-risk variants. For this situation, which is a public health emergency, it is important to vaccinate patients with immunodeficiency and to prevent chronic COVID-19 [16]. Providing information to patients and healthcare professionals about immunodeficiency and COVID-19 vaccination may increase this rate.

In a study of 730 consecutive unvaccinated patients hospitalized in Poland; the most common reasons for vaccine refusal were, concerns about advers effects, believing that the vaccine has not been adequately tested, and believing that one will not get sick with COVID-19 [17]. In our study, the three most common known reasons for not being vaccinated were found to be fear of allergy, fear of advers effects, and distrust of the vaccine, respectively.

Although the COVID-19 vaccine is recommended during pregnancy, the vaccine has lagged behind those who are not pregnant at the same age in pregnant women. As of February 2022, 68% of pregnant people are thought to have completed their primary COVID-19 vaccine [18]. In our study, 6.6% of the patients were not vaccinated due to pregnancy-breastfeeding.

In the study, which included 113 patients with a COVID-19 vaccine reaction, 86.7% of the vaccine reactions occurred in women. Anaphylaxis was observed only in women, all of these patients had a history of allergic disease and two-thirds of them were diagnosed with asthma [2]. The mean age of 12 patients with delayed systemic urticaria reaction following mRNA COVID-19 vaccine was 52 years. 75% of patients were female, 50% had drug allergy and one had a history of chronic spontaneous urticaria [19]. Allergic reactions due to vaccine were observed in 10 of our patients and as in other studies, the majority (%80) were women. 80% of all patients had a history of allergic disease and 40% had a history of drug allergy, which was similar to the studies in the literature. Although extremely rare, cases of vaccine-induced anaphylaxis have been reported in the literature, confirming their safety without a higher mortality rate than previous vaccines [20, 21]. Anaphylaxis with inactivated COVID-19 vaccine is extremely rare, case series involving 12 patients are available in the literature [22]. While anaphylaxis with inactivated vaccine was not observed in our study, anaphylaxis with mRNA vaccine was observed in 2 patients. It was observed that most of the patients who described an allergic reaction to the m-RNA vaccine were revaccinated safely after allergy and immunology evaluation [2]. In addition, it is reported in the literature that two patients who experienced anaphylaxis with the first dose of m-RNA vaccine were able to receive the vaccine successfully with the graded dose increase protocol [23]. This shows that immunologists and allergists play a key role in the COVID-19 vaccine program.

5. Conclusion

In conclusion, 16.9% of the patients who admitted to the immunology and allergy outpatient clinic were never vaccinated, while the rate of those who did not receive two doses of vaccine was 26.6%. The top three reasons for not being vaccinated were fear of allergies, fear of advers effects, and distrust of the vaccine, respectively. The limitations of our study were being retrospective and covering a certain time period and a certain population admitted to the immunology and allergy outpatient clinic. Information about COVID-19 vaccines and reasons for vaccine refusal can be obtained from larger studies with longer follow-up. In this context, understanding the causes of vaccine hesitations at different times in different populations and increasing the vaccination rate by organizing public health campaigns is an important point in the control of the pandemic. In addition, it is important to refer patients who describe an allergic reaction with the COVID-19 vaccine to an immunology and allergy specialist.

Statement of ethics

The study protocol was approved by the local Ethics Committe of Gaziantep University, Gaziantep Turkey (No: 2022/126).

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

Concept/Design, data acquisition, data analysis and interpretation, drafting manuscript: ME, SSM

References

1.Turner PJ, Ansotegui IJ, Campbell DE, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J 2021; 14: 100517. https://doi.org/10.1016/j.waojou.2021.100517

2.Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell Health experience. Ann Allergy Asthma Immunol 2022; 128: 161-168 e161. https://doi.org/10.1016/j.anai.2021.10.019

3.Erdeljic Turk V. Anaphylaxis associated with the mRNA COVID-19 vaccines: Approach to allergy investigation. Clin Immunol 2021; 227: 108748. 20210428. HTTPS://DOİ.ORG/ 10.1016/j.clim.2021.108748.

4.Barbaud A, Garvey LH, Arcolaci A, et al. Allergies and COVID-19 vaccines: An ENDA/EAACI Position paper. Allergy, 2022/02/04. https://doi.org/10.1111/all.15241

5.Mewhirter J, Sagir M and Sanders R. Towards a predictive model of COVID-19 vaccine hesitancy among American adults. Vaccine 2022; 40: 1783-9. https://doi.org/10.1016/j.vaccine.2022.02.011

6.Storey D. COVID-19 Vaccine Hesitancy. Glob Health Sci Pract 2022; 10 20220301. https://doi.org/10.9745/GHSP-D-22-00043

7.Ikiisik H, Akif Sezerol M, Tasci Y, et al. COVID-19 vaccine hesitancy: A community-based research in Turkey. Int J Clin Pract 2021; 75: e14336. 20210526. https://doi.org/10.1111/ijcp.14336

8.Salali GD and Uysal MS. COVID-19 vaccine hesitancy is associated with beliefs on the origin of the novel coronavirus in the UK and Turkey. Psychol Med 2020: 1-3. 20201019. https://doi.org/10.1017/S0033291720004067

9.Koh SWC, Tan HM, Lee WH, et al. COVID-19 Vaccine Booster Hesitancy among Healthcare Workers: A Retrospective Observational Study in Singapore. Vaccines (Basel) 2022; 10 20220317. https://doi.org/10.3390/vaccines10030464

10.Mekonnen BD and Mengistu BA. COVID-19 vaccine acceptance and its associated factors in Ethiopia: A systematic review and meta-analysis. Clin Epidemiol Glob Health 2022; 14: 101001. 20220307. https://doi.org/10.1016/j.cegh.2022.101001

11.Patwary MM, Alam MA, Bardhan M, et al. COVID-19 Vaccine Acceptance among Low- and Lower-Middle-Income Countries: A Rapid Systematic Review and Meta-Analysis. Vaccines (Basel) 2022; 10 20220311. https://doi.org/10.3390/vaccines10030427

12.Ionescu TC, Fetecau BI, Giurgiuca A, et al. Acceptance and Factors Influencing Acceptance of COVID-19 Vaccine in a Romanian Population. J Pers Med 2022; 12 20220313. https://doi.org/10.3390/jpm12030452

13.Sypsa V, Roussos S, Engeli V, et al. Trends in COVID-19 Vaccination Intent, Determinants and Reasons for Vaccine Hesitancy: Results from Repeated

Cross-Sectional Surveys in the Adult General Population of Greece during November 2020-June 2021. Vaccines (Basel) 2022; 10 20220318. https://doi.org/10.3390/vaccines10030470
14.Moscardino U, Musso P, Inguglia C, et al. Sociodemographic and psychological correlates of COVID-19 vaccine hesitancy and resistance in the young adult population in Italy. Vaccine 2022,2022/03/21. https://doi.org/10.1016/j.vaccine.2022.03.018
15.Coulaud PJ, Ablona A, Bolduc N, et al. COVID-19 vaccine intention among young adults: Comparative results from a cross-sectional study in Canada and France. Vaccine 2022:20220303. https://doi.org/10.1016/j.vaccine.2022.02.085
16.Ameratunga R, Longhurst H, Steele R, et al. Common Variable Immunodeficiency Disorders, T-Cell Responses to SARS-CoV-2 Vaccines, and the Risk of Chronic COVID-19. J Allergy Clin Immunol Pract 2021; 9: 3575-83. https://doi.org/10.1016/j.jaip.2021.06.019
17.Zarebska-Michaluk D, Rzymski P, Moniuszko-Malinowska A, et al. Does Hospitalization Change the Perception of COVID-19 Vaccines among Unvaccinated Patients? Vaccines (Basel) 2022; 10 20220319. https://doi.org/10.3390/vaccines10030476
18.Kharbanda EO and Vazquez-Benitez G. COVID-19 mRNA Vaccines During Pregnancy: New Evidence to Help Address Vaccine Hesitancy. JAMA 2022 2022/03/25. https://doi.org/10.1001/jama.2022.2459
19.Pitlick MM, Joshi AY, Gonzalez-Estrada A, et al. Delayed systemic urticarial reactions following mRNA COVID-19 vaccination. Allergy Asthma Proc 2022; 43: 40-3. https://doi.org/10.2500/aap.2022.43.210101
20.Castells M, Demoly P and Tanno LK. [Anaphylaxis and COVID-19 vaccines]. Rev Fr Allergol (2009) 2021; 61: 8S30-38S35. https://doi.org/10.1016/S1877-0320(21)00439-5
21.Armstrong L and Maguire N. A Case Report of Prolonged Anaphylaxis after COVID-19 Vaccine. Clin Pract Cases Emerg Med 2022; 6: 21-4. https://doi.org/10.5811/cpcem.2021.9.53690
22.Laisuan W, Wongsa C, Chiewchalermsri C, et al. CoronaVac COVID-19 Vaccine-Induced Anaphylaxis: Clinical Characteristics and Revaccination Outcomes. J Asthma Allergy 2021; 14: 1209-15. https://doi.org/10.2147/JAA.S333098
23.Cahill JA, Kan M. Successful administration of second dose of BNT162b2 COVID-19 vaccine in two patients with potential anaphylaxis to first dose. Allergy 2022; 77: 337-8. https://doi.org/10.1111/all.14996

Effect of Biochanin-A on the Cerebellum in Cerebral Ischemia Reperfusion Injury

Öner Avınca[1], Özge Kaplan[2], Fırat Aşır[3]

1 Health Sciences University, Gazi Yasargil research and training Hospital, Emergency Department, Diyarbakır, Türkiye
2 Department of Histology and Embryology, Kocaeli City Hospital, Kocaeli, Türkiye
3 Department of Histology and Embryology, Medical School, Dicle University, Diyarbakır, Türkiye

Abstract

Aim: To examine the protective effect of Biochanin A (BCA) on the cerebellum in cerebral ischemia reperfusion injury.

Methods: 24 Wistar albino female rats were divided into 3 groups. Control, Ischemia reperfusion (IR), IR +BCA (20 mg/kg intraperitoneal) group. A micro bulldog clamp was placed on the left common carotid artery of the rats and cerebral ischemia was applied for 2 hours. After cerebral ischemia, the clamp was removed and reperfusion was performed for 24 hours. After 7 days, all rats were decapitated and the protective effects of BCAon the cerebellum were evaluated by immunohistochemically analyses.

Results: In the IR group; S100 expression was also observed positive in neurons and neuroglia in the pia mater, molecular layer, Purkinje cells in the ganglionic layer and granule cells in the granular layer, and neuroglia in the white matter. In the IR+ BCA group, it was observed that the immune activity in the granule cells and Purkinje cells in the granular layer was reduced compared to the IR group.

Conclusions: We suggest that BCA treatment has a potential therapeutic role in alleviating inflammation in the cerebellum after cerebral ischemia reperfusion.

Keywords: *Cerebral ischemia, Biochanin A, S100, cerebellum*

1. Introduction

Stroke is the second cause of death and a major cause of disability worldwide[1]. It is examined in two types: ischemic stroke and hemorrhagic stroke. Hemorrhagic stroke is less common[2]. Ischemic stroke is a condition in which the cerebral artery is suddenly blocked by a thrombus and the brain remains hypoxic. Reperfusion is the restoration of blood flow to the ischemic area. This situation increases oxidative stress and inflammation, causing increased neuronal damage. This is called cerebral ischemia/reperfusion injury[3].

Stroke treatments include recanalization and neuroprotection[4] . Today, functional disorders are significantly reduced by using thrombolytic agents and intravascular techniques. Restoration of blood flow and oxygenation often leads to exacerbation of cerebral tissue damage and deepening of the inflammatory response[5].Cerebral ischemia/reperfusion (I/R) is a serious condition that causes cerebral edema, cerebral hemorrhage, and neuronal death. Mechanisms causing cerebral ischemia/reperfusion injury (I/R); Increase in intracellular Ca2+ level, production of free oxygen radicals, increase in pro-inflammatory cytokines, inflammation and apoptosis[6]. Recently, data from many studies have supported the idea that I/R triggers inflammatory cascades in the brain that can further increase tissue damage[6,7]. Upregulation of proinflammatory cytokines occurs within minutes of occlusion. Therefore, effectively preventing and controlling cerebral I/R is of great clinical value [8]. Many structural and biochemical changes can be observed in rats exposed to cerebral ischemia reperfusion, not only in the brain but also in regions far from the ischemic focus. The cerebellum is one of these areas. Apoptosis and inflammation indicate the effects on the cerebellum[9,10].

Phytoestrogens, whose chemical structure is similar to mammalian estrogen, selectively bind to estrogen receptors (ERs) exert estrogenic , anti-estrogenic effects[11,12]. Phytoestrogens are known to be useful in various neurodegenerative disorders such as acute ischemic stroke[13].

BCA (C16H1205) is a phytoestrogen isolated from red clover, chickpeas or other legumes and is an O-methylated natural isoflavonoid. The studie has shown that BCA reduces inflammatory mediators and has a cytoprotective effect[12]. In addition, it is thought that BCA produces neuroprotective effects by inhibiting the inflammatory response in rats subjected to cerebral ischemia/reperfusion, especially as a result of the suppression of p38 signaling pathways[14]. BCA, one of the promising agents in the treatment of

Corresponding Author: Öner Avınca, droneravinca@gmail.com, *Received: 25.01.2024, Accepted: 06.03.2024, Available Online Date: 11.03.2024 Cite this article as: Avinca Ö, Kaplan Ö, Aşır F. Effect of Biochanin-A on the Cerebellum in Cerebral Ischemia Reperfusion Injury. J Cukurova Anesth Surg. 2024; 7(1): 47-51. https://doi.org/10.36516/jocass.1425526*

ischemic stroke patients, needs further investigation.

In our study; we aimed to investigate the protective effects of BCA on the cerebellum in cases of experimental cerebral ischemia reperfusion damage.

2. Materials and methods

2.1 Animals

Our study received ethics number 646615 and 2024/01 date by Dicle University animal experiments local ethics committee. After the rats were divided into 3 equal groups (n:8), general anesthesia was administered with the rats using 90 mg/kg ketamine hydrochloride and 10 mg/kg xylazine (intramuscular) after a 6-hour fast before the operation

The rats were fixed and the neckline was cleaned with povidone-iodine. Common carotid artery was reached. A micro bulldog clamp was placed approximately 1 cm proximal to the left common carotid bifurcation, common carotid artery occlusion was performed, and cerebral ischemia was applied for 2 hours. After cerebral ischemia, the clamp was removed and the tissues were placed in their old anatomical location. The skin and subcutaneous fascia were sutured and the cerebral tissues were reperfused for 24 hours.

2.2 Experimental Groups

1. Control group: Cerebral artery occlusion will not be performed. Only the left common carotid artery will be isolated and the tissues will be closed again. Animals will be given 1 cc of DMSO intraperitoneal for 7 days.

2. Ischemia-Reperfusion (IR) group: Cerebral IR procedure will be applied. Animals were given 1 cc of DMSO intraperitoneal for 7 days.

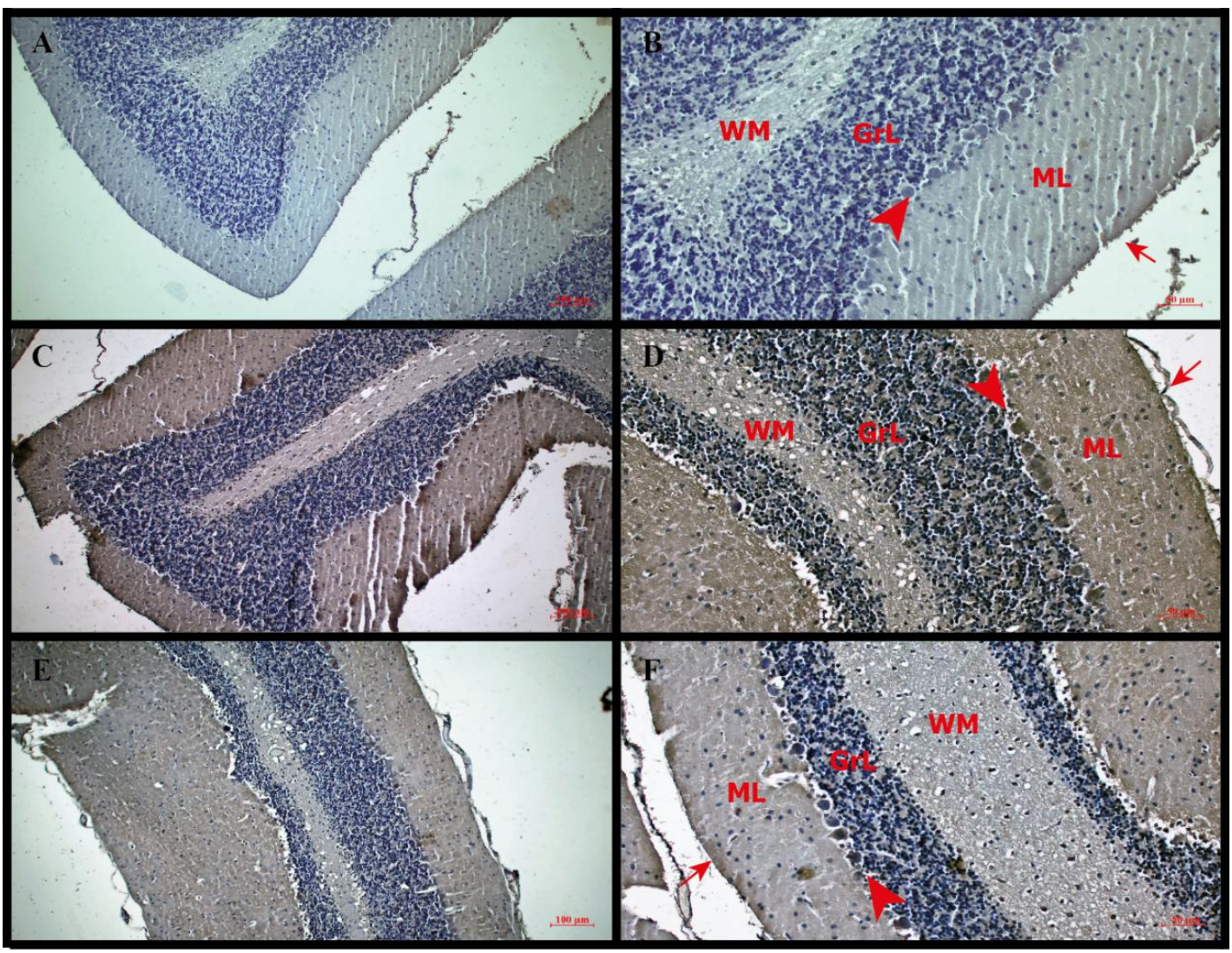
3. IR +BCA group: After the IR procedure, 20 mg/kg BCA was given to the animals intraperitoneal for 7 days. After the experimental protocol was completed (at the end of the 7th day), the animals were sacrificed by drawing blood from the heart under general anesthesia. Cerebellar tissue of rats was removed.

2.3 Histological Tissue Protocol

The collected cerebellum tissue was fixed in chain formalin and subjected to routine histological follow-up. After fixation, alcohol series, xylene and paraffin processes, the tissues were embedded in paraffin blocks. Paraffin blocks were cut to 5 microns using a microtome and a slide was taken. Immunohistochemically staining was performed by applying S100 antibody to the sections.

Figure 1

S100 immune staining of cerebellum tissue sections



2.4 Immunohistochemically staining

Sections of the cerebellum were dewaxed, passed through an alcohol series, and washed with distilled water. 3% hydrogen peroxide (H2O2) was used to block endogenous peroxidase activity. The sections were washed in PBS and then immersed in blocking solution. Before washing, the solution was decanted and the sections were incubated with primary antibody S100 (catalog no: Santa Cruz Biotechnology Inc. CA, USA) overnight at +4°C. Sections were biotinylated and then reacted with streptavidin peroxidase for 15 min. Diaminobenzidine (DAB) chromogen was used as a chromogen to observe the color change after PBS washing. Reactions were stopped with PBS solution and sections were counterstained with hematoxylin dye. Slides were viewed with a Zeiss Imager A2 light microphone. All images were processed and quantified using Image software[15].

2.5 Images Analysis

The staining intensity of S100 expression was measured by Image J software (version 1.53, http://imagej. nih.gov/ij). Measurement was calculated by the method of Crowe et al[16].Quantification was recorded by analyzing ten fields from each specimen per group[17]. In specimens, the brown color stands for the positive expression of the antibody of interest while the blue color represents a negative expression of the antibody of interest. Signal intensity (expression) from a field was calculated by dividing the intensity of the antibody of interest by the whole area of the specimen. A value for staining area/whole area was calculated for each specimen from ten fields. An average value was measured for groups and analyzed for semi-quantitative immunohistochemistry scoring.

2.6 Statistical Analysis

IBM SPSS 25.0 software (IBM, Armonk, New York, USA) was used for statistical analysis. The data were recorded as median (quartile 25 and quartile 75). Shapiro-Wilk test was used to evaluate statistical distribution. Multiple group comparisons were done with the Kruskal wallis and posthoc Dunn's test. Significance was considered for p-values<0.05.

Figure 2

Negative Control of S100 immune staining of cerebellar sections. A: 100 µm, magnification: 10X; B: 50 µm, magnification: 20X

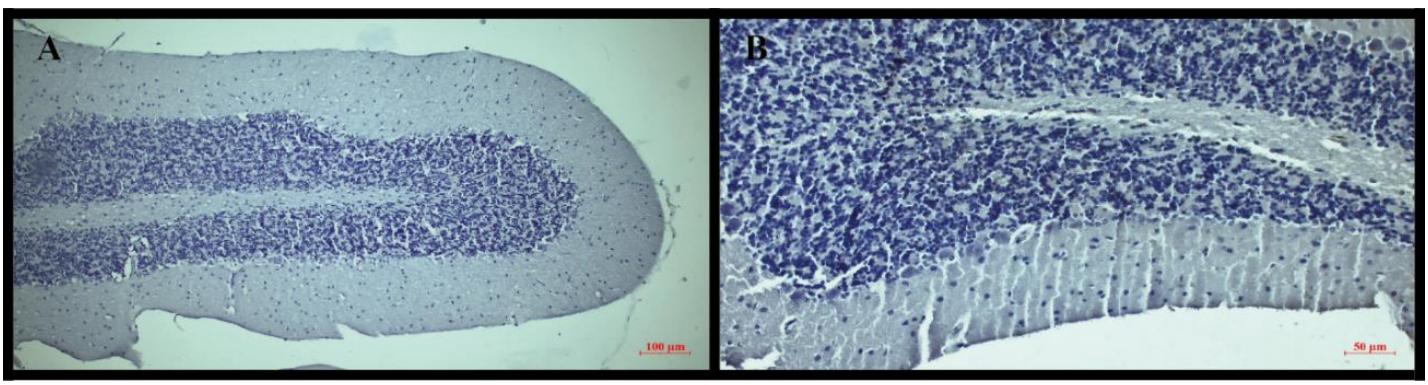


Figure 3

Graphical illustration of signal intensity

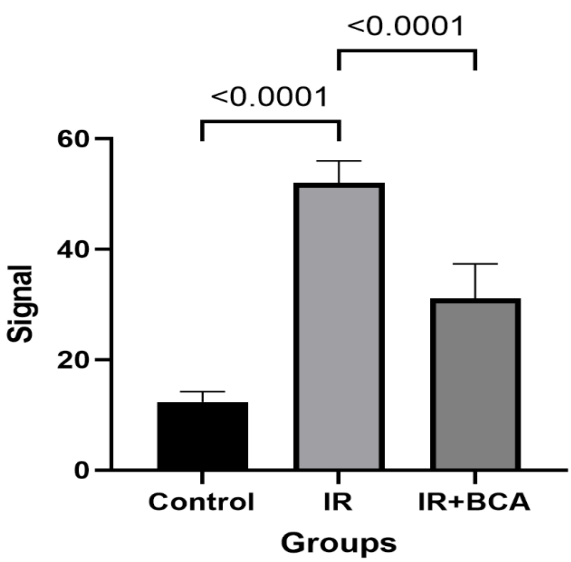


Table 1

S100 signal level in groups

	Control	IR	IR+BCA
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)
S100 signal	12 (11-14)	48 (52-55)*	32 (25-37)**

3. Results

3.1 Immunohistochemically Findings

S100 immune staining of cerebellum tissue sections is shown in Figure 1. In the images of the control group, S100 expression was observed to be negative in the white matter, granular layer, ganglionic layer and molecular layer (Figure 1a and 1b). S100 expression generally increased due to inflammation after cerebral ischemia reperfusion (IR). Increased S100 expression was observed in neurons and neuroglia in the pia mater, molecular layer, Purkinje cells in the ganglionic layer, and granule cells in the granular layer, compared to the control group. S100 expression was also observed positive in neuroglia in the white matter (Figure 1c and 1d). After BCA treatment, S100 expression decreased in the cerebellum tissue due to the anti-inflammatory properties of BCA. It was observed that immune activity, especially in the granule cells and Purkinje cells in the

granular layer, decreased compared to the IR group (Figure 1e and 1f).

Figure 1. Cerebellar sections of control (a and b), IR (c and d) and IR+BCA (e and F) groups. WM: white matter, GrL: granular layer, ML: molecular layer, arrow: pia-mater, arrowhead: Ganglionic layer (Purkinje cells). A, C and E: 100 µm, magnification: 10X; B, D and F: 50 µm, magnification: 20X,

Figure 2. negative Control of S100 immune staining of cerebellar sections. A: 100 µm, magnification: 10X; B: 50 µm, magnification: 20X

3.2 Statistical Findings:

Semiquantitative measurement of S100 immune staining was shown in Table 1. Graphical illustration of signal intensity was shown in Figure 3 with significance.

4. Discussion

Ischemia (I) is the hypoxic effect that occurs when there is no or little blood flow in tissues and organs. Reperfusion (R) is the resumption of blood flow. Both situations are dangerous. The harmful effects of free oxygen radicals (ROS) formed as a result of ischemia increase with the reperfusion into the tissues during the reperfusion phase.[18]. The brain is one of the most important organs to be affected by ischemia reperfusion. In cerebral ischemia/reperfusion (I/R) injury, serious conditions such as brain edema, brain hemorrhage and neuron death may occur[14].

Structural and biochemical changes can also be observed of outside ischemic area in animals exposed to cerebral ischemia[19]. The studie has shown that the cerebellum is one of the affected areas. Edema occurring in the brain after ischemia in animals compresses the cells in the contralateral hemisphere. Increased intracellular calcium indirectly causes metabolic stress. As a result, various inflammatory mediators, growth factors and heat shock proteins are induced[19].

S100 proteins are known to be a family of low-molecular-weight calcium-binding proteins found in vertebrates. S100 B protein, which belongs to th5-3 e S100 family, is released by astrocytes in the brain[20]. Trophic or apoptotic depending on the level of secretion leads to results. This toxic effect of S100 is based on its ability to induce pro-inflammatory cytokines, oxidative stress enzymes, especially iNOS 31-35[21]. Sun at all. showed that proteins belonging to the S100 family were upregulated in the brains of mice in which focal cerebral ischemia caused reperfusion[22].

In our study, we chose the S100 antibody to examine the inflammation in the cerebellum tissue of rats in which we created cerebral ischemia reperfusion. That S100 expression was negative in the white matter, granular layer, ganglionic layer and molecular layer in the images of the control group (Figures 1a and 1b), S100 expression generally increased due to inflammation after cerebral ischemia reperfusion (IR). Increased S100 expression was observed in neurons and neuroglia in the pia mater, molecular layer, Purkinje cells in the ganglionic layer, and granule cells in the granular layer, compared to the control group. We also observed positive S100 expression in neuroglia in the white matter (Figures 1c and 1d).

BCA is a type of phytoestrogen that shows anti-tumorigenesis, anti-oxidation, anti-inflammatory and hypoglycemic effects. Recently, various studies have been conducted to examine the effects of BCA on cerebral ischemia reperfusion. In a study, BCA was used to inhibit the inflammatory response in rats with cerebral ischemia/reperfusion injury, and BCA showed a neuroprotective effect by suppressing inflammation[14]. BCA reduced cerebral ischemia reperfusion injury by reducing leukocyte migration [23].

In the study, in the cerebellum of rats in the ischemia reperfusion + BCA group; We observed that immune activity in granule cells and Purkinje cells in the granular layer was reduced compared to the IR group (Figures 1e and 1f).

5. Conclusion

The results indicate that BCA treatment exerts anti-inflammatory effects in cerebellum tissue following cerebral ischemia-reperfusion. The observed decrease in S100 expression, especially in key cell types, suggests a potential therapeutic role for BCA in mitigating inflammation associated with cerebral IR injury. Further studies and analyses may be needed to explore the underlying mechanisms and to validate the potential clinical relevance of these findings

Statement of ethics

Our study received ethics number 646615 and 2024/01 date by Dicle University animal experiments local ethics committee.

Conflict of interest statement

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

Funding source

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

All authors contributed equally to the article. All authors read and approved the final manuscript.

References

1.Katan M, Luft A. Global burden of stroke. Thieme Medical Publishers; 2018:208-11.
https://doi.org/10.1055/s-0038-1649503
2.Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurologic clinics. 2008;26(4):871-95.
https://doi.org/10.1016/j.ncl.2008.07.003
3.Nagy Z, Nardai S. Cerebral ischemia/repefusion injury: From bench space to bedside. Brain research bulletin. 2017; 134:30-7.
https://doi.org/10.1016/j.brainresbull.2017.06.011
4.Eltzschig HK, Eckle T. Ischemia and reperfusion-from mechanism to translation. Nature medicine. 2011;17(11):1391-401.
https://doi.org/10.1038/nm.2507
5.Durukan A, Tatlisumak T. Acute ischemic stroke: overview of major experimental rodent models, pathophysiology, and therapy of focal cerebral ischemia. Pharmacology Biochemistry and Behavior. 2007;87(1):179-97.
https://doi.org/10.1016/j.pbb.2007.04.015
6.Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. Journal of translational medicine. 2009;7(1):1-11.
https://doi.org/10.1186/1479-5876-7-97
7.Majid A. Neuroprotection in stroke: past, present, and future. International Scholarly Research Notices. 2014;2014
https://doi.org/10.1155/2014/515716
8.Jurcau A, Simion A. Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: from pathophysiology to therapeutic strategies. International journal of molecular sciences. 2021;23(1):14.
https://doi.org/10.3390/ijms23010014
9.Gilmore W, Chikritzhs T, Stockwell T, et al. Alcohol: taking a population perspective. Nature Reviews Gastroenterology & Hepatology. 2016;13(7):426-34.
https://doi.org/10.1038/nrgastro.2016.70
10.Carvalho CA, Tirapelli DP, Rodrigues AR, et al. Morphological and immunohistochemical analysis of apoptosis in the cerebellum of rats subjected to focal cerebral ischemia with or without alcoholism model. Acta Cirúrgica Brasileira. 2016; 31:629-37.
https://doi.org/10.1590/S0102-865020160090000009

11.Dawson DA, Martin D, Hallenbeck JM. Inhibition of tumor necrosis factor-alpha reduces focal cerebral ischemic injury in the spontaneously hypertensive rat. Neuroscience letters. 1996;218(1):41-4.
https://doi.org/10.1016/0304-3940(96)13116-5
12.Guo M-m, Qu S-b, Lu H-l, et al. Biochanin A alleviates cerebral ischemia/reperfusion injury by suppressing endoplasmic reticulum stress-induced apoptosis and p38MAPK signaling pathway in vivo and in vitro. Frontiers in endocrinology. 2021; 12:646720.
https://doi.org/10.3389/fendo.2021.646720
13.Wang Y, Dong X, Li Z, et al. Downregulated RASD1 and upregulated miR-375 are involved in protective effects of calycosin on cerebral ischemia/reperfusion rats. Journal of the neurological sciences. 2014;339(1-2):144-8.
https://doi.org/10.1016/j.jns.2014.02.002
14.Wang W, Tang L, Li Y, et al. Biochanin A protects against focal cerebral ischemia/reperfusion in rats via inhibition of p38-mediated inflammatory responses. Journal of the neurological sciences. 2015;348(1-2):121-5.
https://doi.org/10.1016/j.jns.2014.11.018
15.Başaran SÖ, Kaplan Ö, Aşır F. Effect of Gallic Acid on Distant Organ Stomach in Intestinal Ischemia Reperfusion Injury. Journal of Drug Delivery and Therapeutics. 2023;13(5):17-21.
https://doi.org/10.22270/jddt.v13i5.6049
16.Crowe AR, Yue W. Semi-quantitative Determination of Protein Expression using Immunohistochemistry Staining and Analysis: An Integrated Protocol. Bio Protoc. Dec 20 2019;9(24) doi:10.21769/BioProtoc.3465
https://doi.org/10.21769/BioProtoc.3465
17.Aşır F, Oğlak SC, Ağaçayak E, et al. Homeobox A Cluster 7 (HOXA7) protein expression increased in the placentas of patients with preterm delivery. Perinatal Journal. 2023;31(3):213-8.
18.Aktaş A, Aşır F, Başaran SÖ, et al. Granulocyte colony stimulating factor (GCSF) protected in ovarian tissues against ischemia-reperfusion injury. Journal of Drug Delivery and Therapeutics. 2022;12(4):26-30.
https://doi.org/10.22270/jddt.v12i4.5538
19.Leker RR, Shohami E. Cerebral ischemia and trauma-different etiologies yet similar mechanisms: neuroprotective opportunities. Brain Research Reviews. 2002;39(1):55-73.
https://doi.org/10.1016/S0165-0173(02)00157-1
20.Deveci E, Aşır F, Başaran SÖ, et al. Evaluation of the Effect of Resveratrol on Hippocampus in Experimental Traumatic Brain Injury. Journal of Drug Delivery and Therapeutics. 2023;13(7):1-5.
https://doi.org/10.22270/jddt.v13i7.6118
21.Bianchi R, Kastrisianaki E, Giambanco I, et al. S100B protein stimulates microglia migration via RAGE-dependent up-regulation of chemokine expression and release. Journal of Biological Chemistry. 2011;286(9):7214-26.
https://doi.org/10.1074/jbc.M110.169342
22.Sun P, Li Q, Zhang Q, Xu L, et al. Upregulated expression of S100A8 in mice brain after focal cerebral ischemia reperfusion. World Journal of Emergency Medicine. 2013;4(3):210.
https://doi.org/10.5847/wjem.j.issn.1920-8642.2013.03.010
23.Fu L, Hu J, Shao F, et al. Biochanin A, as the Lrg1/TGF-β/Smad2 pathway blockade, attenuates blood-brain barrier damage after cerebral ischemiareperfusion by modulating leukocyte migration patterns. Biocell. 2023;47(8)
https://doi.org/10.32604/biocell.2023.028602