Year April 2025
Volume 16
Issue 54

INTERDISCIPLINARY MEDICAL JOURNAL

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2025;16(54)

EDITORIAL BOARD

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2025;16(54)

EDITORIAL BOARD

Institutional Contact

E mail: tip.dergi@mku.edu.tr

Hatay Mustafa Kemal University, Tayfur Ata Sökmen Faculty of Medicine, Dean's Office

31100 Hatay, Türkiye

☎ Phone: +90(326)2213317 📠 Fax: +90(326)2213320

Journal's History

Journal's Previous Name	Parallel Title	ISSN	Years
Mustafa Kemal Üniversitesi Tıp Fakültesi Dergisi	Medical Journal of Mustafa Kemal University	1308-7185	2010-2014
Mustafa Kemal Üniversitesi Tıp Dergisi	Medical Journal of Mustafa Kemal University	2149-3103	2015-2022

INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2025;16(54)

ADVISORY BOARD

iii

INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2025;16(54)

ADVISORY BOARD

iv

ADVISORY BOARD

v

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2025;16(54)

INDEXED BY

TUBITAK TR INDEX

Türkish Medline

Turkish Citation Index

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.
The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).
In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Interdisciplinary Medical Journal
Volume 16, Issue 54, April 2025
Owner: Dean, Prof. Dr. Cahit Özer on behalf of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine
Publisher: Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine
Managing Editor: Enver Sedat Borazan
Address: Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine Dean's Office, 31100 Hatay, Türkiye
E-mail: tip.dergi@mku.edu.tr
Online Publication Date: April, 2025, Hatay
Frequency: Published online three times a year on April, August, and December.

Design and Typesetting: Dr. Uğur Koçak

vi

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2025;16(54)

ABOUT

Interdisciplinary Medical Journal is an open access scientific journal, which publishes original contributions in clinical disciplines pertaining to human medicine. In this context, the Journal publishes original research, case reports and reviews based on clinical studies having interdisciplinary approach on medicine. The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. The manuscript evaluation is based on the principles of blind peer-review process. It is published online three times a year on April, August, and December. The communication, review and publication language of the Journal is English. Manuscripts submitted for publication in the journal should be prepared in accordance with research and publication ethics. All manuscripts should be submitted by online system of the Journal. All manuscripts submitted to the Journal are screened in terms of originality.

Focus & Scope

Interdisciplinary medicine can be defined as "an interdisciplinary approach that relies on health professionals from different disciplines, along with the patient, working collaboratively as a team. The most effective teams share responsibilities and promote role interdependence while respecting individual members' experience and autonomy.

By supporting the interdisciplinary research on medicine, The Journal aims to;

Publish original contributions from different scientific disciplines through the advisory board covering a wide range of clinical medical disciplines,

Offer all its content freely available without charge to the user or his/her institution, to make research freely available to the public, and to support a greater global exchange of knowledge,

By permitting authors to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), to lead productive exchanges, as well as earlier and greater citation of published work.

Subject areas include, but are not restricted to the **clinical studies** of the following fields:

First Aid and Emergency Medicine

Family Medicine

Public Health and Preventive Medicine

Internal Diseases

General Surgery

Gynecology and Obstetrics

Ear, Nose and Throat Diseases

Eye Diseases

Orthopedics and Traumatology

Radiology and Radiodiagnostics

Anesthesia and Intensive Care Medicine

Adolescent Diseases

Childhood Diseases

Multisystem Diseases

Physical Medicine and Rehabilitation

Forensic Medicine

Mental Health and Diseases

Cardiovascular System Diseases

Nervous System Diseases

Neurosurgery

Respiratory System Diseases

Infectious Diseases

Occupational Diseases

Nuclear Medicine

Oncological Diseases

Sports Medicine

Genetic Diseases

Medical Pathology

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Abstracting and Indexing

Interdisciplinary Medical Journal is indexed by TÜBITAK TR Index, Turkish Medline, Turkish Citation Index, and Index Copernicus World of Journals

Editorial Policy

The editorial and publication processes of the journal are shaped in accordance with the guidelines of The International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of

vii

Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

Peer-Review Policy

Initial Manuscript Evaluation

For consideration, all manuscripts should be submitted by online system of The Journal at https://dergipark.org.tr/en/pub/interdiscip. The whole editorial process of The Journal is done via online submission system and can be documented in case of a conflict or objection.

The suitability of papers for publication in The Journal is decided by the editorial policy of the editorial board.

Editor-in-Chief is fully authorized for reviewing process, which is processed in the order of submission to The Journal.

Editor-in-Chief assigns either one of the Co-Editors or himself in order to perform initial assessment. Then, the assignee conducts initial pre-refereeing checks to ensure the article is legible, complete, correctly formatted, original, within the scope of The Journal, in the style of a scientific article and written in clear language.

Ethical Declaration

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential. Informed consent should be obtained in human studies and it should be stated in the manuscript.

Human and Animal Rights: For the experimental, clinical and drug human studies, approval by ethical committee and a statement on the adherence of the study protocol to the international agreements (World Medical Association Association of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended October 2013, www.wma.net) are required. In experimental animal studies, the authors should indicate that the procedures followed were by animal rights (Guide for the care and use of laboratory animals, https://nap.nationalacademies.org/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals), and they should obtain animal ethics committee approval. The Ethics Committee approval document should be submitted to the The Bulletin of Legal Medicine together with the manuscript.

The approval of the ethics committee, statement on the adherence to international guidelines mentioned above and that the patient's informed consent is obtained should be indicated in the Method section and is required for case reports whenever data/media used could reveal the identity of the patient. The declaration of the conflict of interest between authors, institutions, acknowledgement of any financial or material support, aid is mandatory for authors submitting a manuscript, and the statement should appear at the end of the manuscript. Reviewers are required to report if any potential conflict of interest exists between the reviewer and authors, institutions.

For persons under 18 years of age, please provide a consent form that includes both parents' signatures or of the person's legal guardian or supervisor.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2013. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Check for Plagiarism

The Journal is a member of Crosscheck, and all manuscripts are screened by Crosscheck in terms of originality. If serious issues are identified concerning the manuscript, the assignee will notify the corresponding author as part of our standard procedure. No action is required from you unless specifically requested for very serious concerns.

Any article that has problems with any of the above criteria may be rejected at this stage. Manuscripts rejected at this stage typically are not in line with the focus and scopes of the journal. Essays that pass through this stage are then entered into the peer review process.

Manuscript Files

This journal follows a double-blind reviewing procedure. Authors are therefore requested to submit; a blinded manuscript, and a separate title page file.

You may download full manuscript and blinded manuscript templates by following the links on Journal's homepage.

1) Blinded Manuscript File: This is the blinded manuscript file that will be presented to the reviewers. The main text of the article, beginning from Abstract till References (including tables, figures or diagrams) should be in this file. The file must not contain any mention of the authors' names or

viii

initials or the institution at which the study was done, ethical committee or acknowledgements. Self-identifying citations and references in the article text should be avoided.

2) Title Page File: Only descriptive parts of the manuscript should be included in this file. General information about the article and authors is presented on the title page file and it should include the article title in English, author information, email address of each (all) author, ORCID iDs, any disclaimers, sources of support, conflict of interest declaration, ethical committee information, contact information of the corresponding author, acknowledgement and authorship contribution. This file will not be shared with reviewers.

The Journal adheres to a strict policy of double-blind, peer-review to ensure best practices in scholarly research and publication. In Double-blind model, the reviewers do not know the names of the authors, and the authors do not know who reviewed their manuscript. To ensure anonymity in the double-blind refereeing process, the author's name should not appear anywhere on the manuscript. If using Microsoft Word, the manuscript 'Summary', under the menu 'File/Properties/Summary', should also be erased. Once blinded, the assignee selects at least two members of the advisory board, and manuscripts are shared with these experts within the field for double-blind peer review, in which both the Reviewer and the Author remain anonymous throughout the process. A reviewer may not belong to the same institution as authors.

After assigned, the reviewers are invited to participate the review process via a notification email. The email invitation to reviewers will contain all necessary information about the manuscript. The reviewers are asked to log into the journal web site to indicate whether they will undertake the review or not, as well as to access the submission and to record their review and recommendation.

Automated email reminders are sent to the reviewer when the reviewer does not respond to a review request within 15 days. The typical period of time allowed for reviews is 4 weeks but note that it can be modified during the editorial process.

Peer Review Reports

Reviewers make one of the following recommendations to the Editors: accept submission, minor revision, major revision, decline submission. Additionally, reviewers are asked to provide significant commentary for authors and are also provided space to make comments intended solely for the editors. Reviewers are not asked or expected to make any copyediting comments.

If both reviewers agree on acceptance or rejection, the decision stands.

Occasionally, we receive contradicting Reviewers' reports and need to ask for a third reviewer, which does delay the process. When their opinions are poles apart, then the Associate Editor takes a further process to decide acceptance or rejection of that paper. For the further process, Associate Editors request an emergency review by another advisory board member. Associate Editors may take a further process for the manuscript of which reviewing process is overdue.

If a paper is not suitable for publication it will be returned to the author with a statement of reasons for rejection. The author may appeal if he or she believes an erroneous or unfair judgment has been made. A letter to the Editor-in-Chief presenting reasons why the decision should be reconsidered will be subjected to due consideration.

After review, the author is notified by email for revision in accord with suggestions made by the reviewers and the Editor.

At the completion of each round of the peer review process, the submitter receives a formal letter from the Editor that includes notes from the Peer Reviewers.

When authors make revisions to their article in response to the referees' comments, they are asked to submit a list of changes and any replies for transmission to the referees. The author must upload the revised manuscript to the online system within 4 weeks; otherwise, the author will be notified that the paper will be considered withdrawn.

The revised version is usually returned to at least one of the original referees who is then asked whether the revisions are satisfactory. If the referees remain dissatisfied, the paper can be referred to the advisory board of the journal for further consideration.

The assignee then, will check if the manuscript is revised as suggested by editorial members and proceed to the next step. If the assignee finds the revisions satisfying, then he or she will record the decision to accomplish the review process and reach final decision.

Decision Making Process

Based upon two or more reviewers' reports, the Co-Editors are responsible for making the decision regarding acceptance or rejection each essay and for communicating this decision to the submitter. At the completion of the peer review process, each submitter receives a formal letter from the Editors that includes notes from the Peer Reviewers.

The final decision by Editor-in-Chief is usually completed within 2 months from the time of the paper submission.

Authors are notified by e-mail when a manuscript has or has not been accepted for publication. Proofs of accepted manuscripts are sent to the author for correction within 4 weeks after acceptance. They should be proofread carefully according to the instructions attached and returned within the considered period. Authors will be charged for major corrections to their proofs.

For 2020, average days required to complete the review process is 120 days, whereas average days that pass till publication is 180 days.

ix

Publication Frequency

Interdisciplinary Medical Journal publishes three issues online in April, August and December. The communication, review and publication language of the Journal is English.

Open Access Policy

The Journal is an open access scientific journal. Open access means that all content is freely available without charge to the user or his/her institution on the principle that making research freely available to the public supports a greater global exchange of knowledge. The Journal and content of this website is licensed under the terms of the Creative Commons Attribution (CC BY) License. This is in accordance with the Budapest Open Access Initiative (BOAI) definition of open access.

Creative Commons

A Creative Commons license is a public copyright license that provides free distribution of copyrighted works or studies. Authors use the CC license to transfer the right to use, share or modify their work to third parties. The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-commercial re-use of an open access article, as long as the author is properly attributed. This journal is licensed under Attribution 4.0 International (CC BY 4.0) which permits third parties to share and adapt the content by giving the appropriate credit to the original work.

In general, you may visit the Journal website and reach full text of any published article without identifying yourself or revealing any personal information.

The Journal requires the author as the rights holder to sign and submit **the journal's agreement form** prior to acceptance. The authors transfer copyright of their work and grant The Journal for its publication. This ensures both that The Journal has the right to publish the article and that the author has confirmed various things including that it is their original work and that it is based on valid research.

Authors who publish with this journal agree to the following terms:

Authors transfer copyright and grant the journal right of first publication with the work simultaneously licensed under a Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in this journal.

Authors are able to enter into separate, additional contractual arrangements for the non-exclusive distribution of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book), with an acknowledgement of its initial publication in this journal.

Authors are permitted and encouraged to post their work online (e.g., in institutional repositories or on their website) prior to and during the submission process, as it can lead to productive exchanges, as well as earlier and greater citation of published work.

Self-Archiving Policy

The Journal is an open access scientific journal, officially published by Hatay Mustafa Kemal University Faculty of Medicine, Dean's office.

The Journal and content of its website is licensed under the terms of the Creative Commons Attribution (CC-BY) License.

The Journal allows authors to self-archive their articles in an open access repository. The Journal considers publishing material where a pre-print or working paper has been previously mounted online. The Journal does not consider this an exception to our policy regarding the originality of the paper (not to be published elsewhere), since the open access repository doesn't have a publisher character, but an archiving system for the benefit of the public.

The Journal's policy regarding the accepted articles requires authors not to mention, in the archived articles in an open access repository, their acceptance for publication in the journal until the article is final and no modifications can be made. Authors are not allowed to submit the paper to another publisher while is still being evaluated for the Journal or is in the process of revision after the peer review decision.

The Journal does allow the authors to archive the final published article, often a pdf file, in an open access repository, after authors inform the editorial office. The final version of the article and its internet page contains information about copyright and how to cite the article. Only this final version of the article is uploaded online, on the Journal's official website, and only this version should be used for self-archiving and should replace the previous versions uploaded by authors in the open access repository.

Article Processing Charge (APC)

All articles published in our journal are open access and freely available online. Currently, the Journal charges no fee from the authors neither for the review of manuscripts nor publication. This is made possible by the financial support of Hatay Mustafa Kemal University. The Journal does not have a commercial income and covers expenses from university budget. The journal is intended to charge no publication fee as long as possible.

Material Disclaimer

Statements or opinions stated in articles published in the journal do not reflect the views of the editors, editorial board and/or publisher; The editors, editorial board and publisher do not accept any responsibility or liability for such materials. All opinions published in the journal belong to the authors.

x

Correspondence Address (Editorial Office):

Interdisciplinary Medical Journal

Hatay Mustafa Kemal University Faculty of Medicine, Dean's office.

Tayfur Sökmen Campus. 31100 Antakya-Hatay, Türkiye

E-Mail: tip.dergi@mku.edu.tr

Phone: 0 326 245 51 14

Online Manuscript Submission: https://dergipark.org.tr/en/pub/interdiscip

Publisher Corresponding Address:

CETUS Publishing

Address: Balıkesir Teknokent Çağış Mah. Çağış B.M.Sk. No:340/16 İç Kapı No:17 Bigadiç/ Balıkesir, Türkiye

Phone: +90 532 605 56 85/+90 850 380 08 02

E-mail: info@cetuspub.com

Website: www.cetuspub.com

Author Guide

Dear author,

Thank you for your interest in submitting your manuscript to Interdisciplinary Medical Journal for editing and publication consideration. In order to facilitate preparation and submission of your manuscript, we have prepared this guideline explaining basic points that should be taken into account when preparing the paper.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.

2. Where available, DOIs for the references list have been provided.

3. During the online submission, I undertake to enter the names of all the authors in the manuscript, their positions, ORCID ID*** information and the contact details of the responsible author.

*** The publication of ORCID ID information of all authors is mandatory by TUBITAK ULAKBIM Index.

4. By 2020, in accordance with the TR Directory Rules, the authors have to submit an official letter with an Ethical Commission report or equivalent for the works requiring ethics committee permission.

5. Blinded manuscript file to be sent to the reviewer,

6. Title page, A separate title page file containing article title; academic titles, areas of expertise, affiliations, and e-mail addresses each author; contact address of the corresponding author, disclaimer, financial resources of the study, information on whether there is a conflict of interest, article title, short title, thanks and authorship contribution.

7. The author agreement form has been signed by the corresponding author and prepared for submission.

Note: After filling the copyright and ethics form downloaded from the website of the journal with Adobe Reader program on the computer, the printout must be signed by the responsible author with a wet signature, as a picture file or as a pdf—the signed paper document can be photographed with a mobile phone or scanned with a scanner. It can be uploaded to the files section.

8. Blinded manuscript file and title page file are in the Microsoft Word file format.

Writing Rules

In order to prevent waste of effort and time, and to evaluate the manuscript drafts you send to Interdisciplinary Medical Journal, you must use Interdisciplinary Medical Journal templates, which you can download to your computer using the links on the journal homepage, and which contain explanations for the writing rules in the comments section.

The Journal is official publication of Hatay Mustafa Kemal University, Faculty of Medicine. It is an open access scientific journal, being published three times a year and peer reviewed. The Journal aims to publish original contributions based on clinical studies having interdisciplinary approach on medicine. The publication language of the journal is English.

Subject areas include, but are not restricted to the **clinical studies** of the following fields: first aid and emergency medicine, family medicine, public health and preventive medicine, internal diseases, general surgery, gynecology and obstetrics, ear, nose and throat diseases, eye diseases, orthopedics and traumatology, radiology and radiodiagnostics, anesthesia and intensive care medicine, adolescent diseases, childhood diseases, multisystem diseases, physical medicine and rehabilitation, forensic medicine, mental health and diseases, cardiovascular system diseases, nervous system diseases, neurosurgery, respiratory system diseases, infectious diseases, occupational diseases, nuclear medicine, oncological diseases, sports medicine, genetic diseases, medical pathology.

The journal covers all relevant branches in **clinical medicine** specialties of the topics mentioned above.

xi

Audience

Academicians, specialist physicians and research assistants in surgical and non-surgical medical disciplines and general practitioners.

Manuscript Preparation

All manuscripts which will be published in the journal must be in accordance with research and publication ethics. All authors should have contributed to the article directly either academically or scientifically. Presentations at congresses or in symposia are accepted only if they were not published in whole in congress or symposium booklets and should be mentioned as a footnote.

Manuscripts are received with the explicit understanding that they have not been published in whole or in part elsewhere, that they are not under simultaneous consideration by any other publication. Direct quotations, tables, or illustrations that have appeared in copyrighted material must be accompanied by written permission for their use from the copyright owner and authors. All articles are subject to review by the editors and referees.

Process of Peer Review

The journal utilizes a standard online site (https://dergipark.org.tr/en/pub/interdiscip), supported by Tubitak Ulakbim, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to the journal, the journal manager and editorial staff review the submission to assure all required components as outlined in this Guide for Authors are included. The manuscript is then assigned to one of the co-editors (either the editor in chief or an associate editor) who directs and oversees the peer-review process. The co-editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made. Acceptance is based on significance, and originality of the material submitted. If the article is accepted for publication, it may be subject to editorial revisions to aid clarity and understanding without changing the data presented.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

About the scientific language to be used in writing your manuscript

In line with the recommendation of the international directories we applied to increase the scientific effectiveness of our journal and enrich its content, our Editorial Board has decided that the studies to be published in English. So, the manuscripts sent to our journal are subject to English language control and revision.

Our experience from previous articles has shown that most of the articles prepared in English need to be improved in terms of fluent readability and intelligibility, as well as scientific and technical examination. Most of the manuscripts should undergo a comprehensive review and revision process in terms of language, before they were included in the review stage.

Therefore, we recommend that you receive professional English editing and proofreading services before submitting your manuscript to our journal, although it is not mandatory.

Our journal does not have any commercial partnership with any translation or proofreading service company, and our authors are absolutely free to make their choices as they wish.

By uploading the revised English full text of your manuscript to our Journal system by ensuring that English Editing and Proofreading is carried out by a local or foreign professional, you may minimize the possibility of rejection due to translation errors.

Use of first person

In addition, it is necessary to make the necessary checks and revisions in terms of language of your work and to ensure integrity in terms of language and time use throughout the entire article.

Expressions such as ... "Our study, in our study, we, we did, we found, we aimed, I did, I found, I think ... etc." should be revised as follows;

- In this study, ... it was found/determined/... or
- In this study ... it was aimed to ...

Names made up of single word should not be abbreviated.

Instead of,

- Hypertension (HT) is one of the most ...

Throughout the manuscript, you should use;

- Hypertension is one of the most ...

Instead of,

- Rituximab (RTX) is an IgG1 kappa chimeric monoclonal

xii

Throughout the manuscript, you should use;

• Rituximab is an ...

Numbers should always be used to indicate statistics, age and measurements (including time as in the 3 weeks example). In specifying the others, only the numbers one to nine should be written in letters. (Numbers between 1-10 should be written with letters, except for the date and number of cases)

For example;

• In 2 studies, ...

Should be replaced with;

• In two studies ...

For example;

• ... perivascular lymphotic infiltration in only 10 percent and fibrosis in 7 percent of the patients,

Should be replaced with;

• ... perivascular lymphotic infiltration in only 10% of patients ... in 7% of patients ...

Prejudiced expressions should be avoided in expressions other than classical textbook knowledge, which has been verified by dozens of studies and has become the industry standard in the literature.

• determined to be high

Should be replaced with;

• ... was found to be high.

Or throughout the entire manuscript;

• found to be significantly higher ...

If diametrically opposite findings are mentioned among the studies mentioned in the Discussion section, it should be stated as "... a significant relationship was found / observed / reported", rather than "a significant relationship was determined" etc.

• While no significant relationship was determined between blood pressure and disease severity (26,27), a strong relationship was determined in some studies (28,29).

Should be replaced with;

While no significant relationship was observed between blood pressure and disease severity (26,27), it was reported that a strong relationship was found in some studies (28,29).

General Principles

The text of articles reporting original research should be divided into Introduction, Method, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

Sections of the manuscript

Article title

The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Information about the study design could be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Please avoid capitalizing all letters of the title and capitalize only the capital letter of first word of the title, proper nouns, proper adjectives. Other words and conjunctions (e.g., and, but, both, or, either, neither, nor, besides, however, nevertheless, otherwise, so, therefore, still, yet, though etc.) should be in small letters. No abbreviations or acronyms should be used within the titles.

Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical method), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Please, do not cite figures, tables or references in the abstract.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. All the articles submitted to the journal require to include abstract in English. Abstracts of original articles should not exceed 250 words.

xiii

Keywords

Three to six words or determinative groups of words should be written below the abstract. Abbreviations should not be used as keywords. Keywords in English should be chosen from MESH (Medical Subject Headings http://www.nlm.nih.gov/mesh) index. Abbreviations cannot be used as keywords, but instead they should be written explicitly. Letters that do not exist in Latin alphabet (e.g., alpha, beta, delta etc.) should be used with their pronunciation.

Examples: carbon monoxide, firearms, sexual abuse, oral mucosa

Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Method

The guiding principle of the Method section should be clarity about how and why a study was done in a particular way. The Method section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results.

The authors should clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), autopsied persons, including eligibility and exclusion criteria and a description of the source population.

In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the method section.

The Method section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Identifying information, including names, initials, or autopsy numbers of the patients/deceased should not be exposed in written descriptions or photographs in no ways. Identifying details should be omitted if they are not essential.

Informed consent should be obtained in human studies, and it should be stated in the manuscript.

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Statistical Analysis

The authors should describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. They should define statistical terms, abbreviations, symbols and should specify the statistical software package(s) and versions used.

Results

You should present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Please, do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Method Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

You should give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. You should restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Please, use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Discussion

It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular,

xiv

distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted but label them clearly.

In-text Citations and References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Laws (e.g., penal code), statutes and regulations are not scientific writings. In addition to being published on the official gazette, since it is published on various internet sites, a reference number should not be given to laws, statutes and regulations. If it is to be cited within the text, the law could be cited by specifying the number of the law, the date and number of publications in the official gazette (e.g., A Review of Article 5 of the Turkish Criminal Penal Code No. 5237). They should not be numbered within the text, or in the reference list.

To minimize citation errors, references can be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Reference list should be numbered consecutively in the order in which they are first mentioned in the text. Roman numerals should be avoided. Identify references in text, tables, and legends by Arabic numerals (1, 2, 3 ... 9, 0) in parentheses. References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals).

If you refer to a work more than once, use the first number also for the second and following references. References to more than one source in the same phrase may be entered like this: (2-4), i.e., references 2 through 4 in the reference list, and (2-4, 8), i.e. the references 2 through 4, plus reference no 8 in the list of references.

Sample for in-text citation:

In a clinical research in healthy individuals, Ellis (25) has studied the sciatic nerve excursion using ultrasound technique.

Wright and Ellis (10) has investigated the excursion of nerves around the elbow joint.

In another and similar cadaveric study by Wright et al (13), the radial nerve median excursion values were 4.1, 8.8, and 0.2, 0.1 mm with motions of shoulder, elbow, wrist and fingers respectively.

Suicide is a major public health problem and globally the second leading cause of death among young adults (1). Studies focusing on how mental health risk factors impact on youth suicidal behaviors suggest that psychopathological symptoms are associated with suicidal behavior (3,4). Adverse effects of H2S on human health vary from local irritation to immediate death depending on the form, concentration, duration and route of exposure (9, 13-15).

Reference Style

The Vancouver system, also known as Vancouver reference style or the author–number system, is a citation style that uses numbers within the text that refer to numbered entries in the reference list. Vancouver style is used by MEDLINE and PubMed. The names "Vancouver system" or "Vancouver style" have existed since 1978. The latest version of the latter is Citing Medicine, per the References > Style and Format section of the ICMJE Recommendations. In 1978, a committee of editors from various medical journals, the International Committee of Medical Journal Editors (ICMJE), met in Vancouver, BC, Canada to agree to a unified set of requirements for the articles of such journals. This meeting led to the establishment of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). Part of the URMs is the reference style, for which the ICMJE selected the long-established author–number principle.

Since the early to mid-2000s, the United States National Library of Medicine (which runs MEDLINE and PubMed) has hosted the ICMJE's "Sample References" pages. Around 2007, the NLM created Citing Medicine, its style guide for citation style, as a new home for the style's details. The ICMJE Recommendations now point to Citing Medicine as the home for the formatting details of Vancouver style.

Interdisciplinary Medical Journal, since the first day of its publication uses the PubMed/NLM reference style. Thus, references list should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Samples of Formatted References for Authors of Journal Articles web page and detailed in the NLM's Citing Medicine, 2nd edition.

According to the Vancouver rules, you can only refer to the literature you have read yourself. If you find anything interesting in a text where it is referred to another text, you must read and refer to the original.

xv

References List

The references list should be ordered numerically in the order in which the references appear in the text.

The journal's name may be abbreviated, according to the abbreviation rules for journal titles. Records retrieved from a search for the full journal title in the National Library of Medicine's search page include the abbreviated title.

Authors' names should be given as surname followed by initials. There should be a space between surname and initials. A maximum of two initials are allowed for each author, they should be entered without spaces or punctuation. Different authors should be separated by a space and a comma. A period (.) should follow the last author's name. If six or more authors, list the first six authors followed by et al.

Only capital letter of the first word of the title, proper nouns, proper adjectives, acronyms, and initialisms should be capitalized.

The most reliable method for calculating the impact factor of our journal and number of citations of articles published in our journal or calculating the number of times your own article is cited in a healthy way, is to add DOIs to the references section. In order to give the DOIs to the articles published in Interdisciplinary Medical Journal, the CrossRef membership application has been completed and all the research articles, case reports, and reviews are being assigned DOIs. For this reason, DOIs need to be added to the References section if available for those references. We hope that the Simple Text Query Form will be helpful in referencing articles published in our journal.

With the help of the Simple Text Query Form web page, which has a link in the full-text template, DOI records need to be added to the sources.

https://apps.crossref.org/SimpleTextQuery

Note: Please, **do not insert Pubmed ID (PMID) or Pubmed Central ID (PMCID) records** to the reference list since they are useless in determining the citation counts.

We place great importance to the addition of DOIs to the references list.

Sample for Journal Article without DOI

Dokgöz H, Kar H, Bilgin NG, Toros F. Forensic Approach to Teenage Mothers Concept: 3 Case Reports. Turkiye Klinikleri J Foren Med 2008;5(2):80-4

Kaufman DM, Mann KV, Miujtjens AM, Van der Vleuten CP. A comparison of standard setting procedures for an OSCE in undergraduate medical education. Academic Medicine 2000;75:267–71.

Sample for Journal Article with DOI

Koçak U, Alpaslan AH, Yağan M, Özer E. Suicide by Homemade Hydrogen Sulfide in Turkey a Case Report. Bull Leg Med. 2016;21(3):189-192. https://doi.org/10.17986/blm.2016323754

Article not in English

Kar H, Dokgöz H, Gamsız Bilgin N, Albayrak B, Kaya Tİ. Lazer Epilasyona Bağlı Cilt Lezyonlarının Malpraktis Açısından Değerlendirilmesi. Bull Leg Med. 2016;21(3):153-158. https://doi.org/10.17986/blm.2016323748

Books and Other Monographs

Personal author(s)

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Editor(s), compiler(s) as author

Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics. 2nd ed. New York: McGraw-Hill; 2002.

Author(s) and editor(s)

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113

Emmerson BT. Gout and renal disease. In: Massry SG, Glassock RJ (Editors). Textbook of Nephrology 1. Baskı, Baltimore: Williams and Wilkins; 1989. p. 756–760.

Conference proceedings

Harnden P, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Article published on the Internet ahead of the print version:

Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15;100(10):3828-31. Epub 2002 Jul 5.

Part of a homepage/Web site [Edited 28 Dec 2016]

American Medical Association [Internet]. Chicago: The Association; c1995-2016 [cited 2016 Dec 27]. Office of International Medicine; [about 2 screens]. Available from: https://www.ama-assn.org/about/office-international-medicine

Thesis

Skrtic L. Hydrogen sulfide, oil and gas, and people's health [Master's of Science Thesis]. Berkeley, CA: University of California; 2006.

Weisbaum LD. Human sexuality of children and adolescents: a comprehensive training guide for social work professionals [master's thesis]. Long Beach (CA): California State University; 2005. 200 p.

xvi

For the reference types not listed here, please visit Samples of Formatted References for Authors of Journal Articles available at Medline Web site (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

It would be appropriate to place the tables at the end of the main text. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text. Give each column a short or an abbreviated heading. In the tables, case counts (n) and percentages (%) should be specified in separate columns, not in the same cell.

Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes and use symbols to explain information if needed. Symbols may be as alphabet letters or such symbols as *, p t> T §). Please, identify statistical measures of variations, such as standard deviation and standard error of the mean.

Illustrations (Figures)

The lexical meaning of figure constitutes a number symbol (numeral, digit), a written or printed character, a diagram or pictorial illustration of textual matter, arithmetical calculation or digits representing an amount when plural. While definition of picture includes a design or representation made by various means (as painting, drawing, or photography), illustration means a picture or diagram that helps make something clear or attractive. Although these terms bear distinctive meanings, they are too often used interchangeably. Thus, we meant them in the same way without distinction.

Digital images

The 300 DPI Story

In the ancient times when digital cameras have not been invented, the photos taken by analogue cameras were used to be printed on photo papers. In order to transfer these photos to the digital environment, they had to be scanned by optical devices called scanners. On the same dates, desktop publishing and printing technology was far beyond the digital photography, and many years had passed since the invention of laser printing technology. Here, several technical terms should be explained to make the concept clearer. DPI is used to describe the resolution number of dots per inch in a digital print and the printing resolution of a hard copy print dot gain, which is the increase in the size of the halftone dots during printing. A dot matrix printer, for example, applies ink via tiny rods striking an ink ribbon, and has a relatively low resolution, typically in the range of 60 to 90 DPI (420 to 280 µm). An inkjet printer sprays ink through tiny nozzles and is typically capable of 300–720 DPI. A laser printer applies toner through a controlled electrostatic charge and may be in the range of 600 to 2,400 DPI. Along with the cheaper memory chips, 1200 dpi printers have been widely available in the consumer market since 2008. Monitors do not have dots but do have pixels. The closely related concept for monitors and images is pixels per inch or PPI. Old CRT type video displays were almost universally rated in dot pitch, which refers to the spacing between the sub-pixel red, green and blue dots which made up the pixels themselves. The DP measurement of a printer often needs to be considerably higher than the pixels per inch (PPI) measurement of a video display in order to produce similar-quality output. This dithered printing process could require a region of four to six dots (measured across each side) in order to faithfully reproduce the color in a single pixel. An image that is 100 pixels wide may need to be 400 to 600 dots in width in the printed output; if a 100×100-pixel image is to be printed in a one-inch square; the printer must be capable of 400 to 600 dots per inch to reproduce the image. The dpi of early model laser printers was 300 to 360, thus scanning images at 300 DPI was a common practice at that time.

In printing, DPI (dots per inch) refers to the output resolution of a printer or imagesetter, and PPI (pixels per inch) refers to the input resolution of a photograph or image. DPI refers to the physical dot density of an image when it is reproduced as a real physical entity, for example printed onto paper. A digitally stored image has no inherent physical dimensions, measured in inches or centimeters. Some digital file formats record a DPI value, or more commonly a PPI (pixels per inch) value, which is to be used when printing the image. This number lets the printer or software know the intended size of the image, or in the case of scanned images, the size of the original scanned object. For example, a bitmap image may measure 1,000 × 1,000 pixels, a resolution of 1 megapixel. If it is labeled as 250 PPI, that is an instruction to the printer to print it at a size of 4 × 4 inches. Changing the PPI to 100 in an image editing program would tell the printer to print it at a size of 10×10 inches. However, changing the PPI value would not change the size of the image in pixels which would still be 1,000 × 1,000. An image may also be resampled to change the number of pixels and therefore the size or resolution of the image, but this is quite different from simply setting a new PPI for the file.

Therefore, an image that is 2048 pixels in width and 1536 pixels in height has a total of 2048×1536 = 3,145,728 pixels or 3.1 megapixels. One could refer to it as 2048 by 1536 or a 3.1-megapixel image. Or you can think of it as a very low-quality image (72 ppi) if printed at about 28.5 inches wide, or a very good quality (300 ppi) image if printed at about 7 inches wide.

Since the 1980s, the Microsoft Windows operating system has set the default display "DPI" to 96 PPI, while Apple/Macintosh computers have used a default of 72 PPI. The choice of 72 PPI by Macintosh for their displays arose from the convenient fact that the official 72 points per inch mirrored the 72 pixels per inch that appeared on their display screens. (Points are a physical

xvii

unit of measure in typography, dating from the days of printing presses, where 1 point by the modern definition is 1/72 of the international inch (25.4 mm), which therefore makes 1 point approximately 0.0139 in or 352.8 µm). Thus, the 72 pixels per inch seen on the display had exactly the same physical dimensions as the 72 points per inch later seen on a printout, with 1 pt in printed text equal to 1 px on the display screen. As it is, the Macintosh 128K featured a screen measuring 512 pixels in width by 342 pixels in height, and this corresponded to the width of standard office paper (512 px ÷ 72 px/in ≈ 7.1 in, with a 0.7 in margin down each side when assuming 8.5 in × 11 in North American paper size (in Europe, it's 21 cm x 30 cm - called "A4")).

In computing, an image scanner—often abbreviated to just scanner, is a device that optically scans images, printed text, handwriting or an object and converts it to a digital image. Although the history of digital cameras dates back to the 1970s, they have become widely used in the 2000s. While the resolution of the first digital camera invented by Kodak was as low as 100 by 100 pixels (0.01 megapixels), the first commercially available digital camera, Fujix DS-1P had a resolution of 0.4 megapixels. On the other hand, modern scanners are considered the successors of early telephotography and fax input devices. The pantelegraph was an early form of facsimile machine transmitting over normal telegraph lines developed by Giovanni Caselli, used commercially in the 1860s, that was the first such device to enter practical service. The history of the first image scanner developed for use with a computer goes back to 1957. Color scanners typically read RGB (red-green-blue color) data from the array. This data is then processed with some proprietary algorithm to correct for different exposure conditions and sent to the computer via the device's input/output interface. Color depth varies depending on the scanning array characteristics but is usually at least 24 bits. High quality models have 36-48 bits of color depth. Another qualifying parameter for a scanner is its optical resolution, measured in pixels per inch (ppi), sometimes more accurately referred to as samples per inch (spi).

Images in web pages, video, and slide shows can be as low as 72 PPI for a static image or 150 PPI if we are going to focus in on the image. For printing, the DPI needs to be larger, with images scanned in at least 300 DPI. The DPI standard for and images to be printed within journals and books is 300 DPI and for museum exhibits, it's 600 DPI.

The most important factors determining image quality of digital images can be considered as pixel dimensions and color depth. Increasing the dpi value of an image by resampling in Photo Editors (e.g., Adobe Photoshop) has no improving effect on its quality, but it lets us to determine target printing size.

For vector images, there is no equivalent of resampling an image when it is resized, and there is no PPI in the file because it is resolution independent (prints equally well at all sizes). However, there is still a target printing size. Some image formats, such as Photoshop format, can contain both bitmap and vector data in the same file. Adjusting the PPI in a Photoshop file will change the intended printing size of the bitmap portion of the data and also change the intended printing size of the vector data to match. This way the vector and bitmap data maintain a consistent size relationship when the target printing size is changed. Text stored as outline fonts in bitmap image formats is handled in the same way. Other formats, such as PDF, are primarily vector formats which can contain images, potentially at a mixture of resolutions. In these formats the target PPI of the bitmaps is adjusted to match when the target print size of the file is changed. This is the converse of how it works in a primarily bitmap format like Photoshop but has exactly the same result of maintaining the relationship between the vector and bitmap portions of the data.

Long story short, it is not technically possible to talk about DPI value for images that were taken by digital cameras or any type of digital images that were transferred to the computer's storage media. The DPI value stored within exif information of images is just a virtual value just to guide the photo editing software and the graphic artist to determine the target printing size of that image.

Requirements for Digital Media

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

Insert menu - Pictures - Related image file in your computer

You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

Due to the reasons explained above, images should be taken by a digital camera of 5 megapixels or more in JPEG, RAW, or TIFF format, and should be inserted in their original form as JPEG, PNG or TIFF files.

Paper-printed images or documents should be scanned at 300 DPI resolution and should be inserted as TIFF, PNG or JPEG files.

Each vector graphic software has its own built-in settings and may have been preset at 72 dpi. So, the document should be created enough big to obtain the image in the desired dimensions. The vector graphics should be exported to a rasterized image format and inserted such as JPEG, PNG or TIFF files.

For X-ray films, CT scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, you should insert high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, we may require deposition of the original photographs of blots on the journal website.

xviii

Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.

Figures should be made as self-explanatory as possible. Titles and detailed explanations belong in the legends— not on the illustrations themselves.

Figures should be numbered consecutively according to the order in which they have been cited in the text.

In the manuscript, legends for illustrations should be in Arabic numerals corresponding to the illustrations. Roman numerals should be avoided. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, you should identify and explain each one clearly in the legend.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Authors must consult the International System of Units (SI).

Authors should add alternative or non-SI units, when SI units are not available for that particular measurement. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Types of paper

Interdisciplinary Medical Journal publishes the following types of articles.

1. Original Articles: Original prospective or retrospective studies **clinical research** in areas relevant to medicine.

The manuscript should contain English abstract, a maximum of 250 words, and the structured abstract should contain the following sections: objective, method, results, and conclusion. Three to six words or determinative groups of words should be written as keywords below the abstract.

The text of articles reporting original research might contain up to 5000 words (excluding abstract, references list and tables) and should be divided into Introduction, Method, Results, and Discussion sections. References list should also be included so that their number does not exceed 50. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles need subheadings within these sections to further organize their content.

2. Review Articles: The authors may be invited to write or should be expert in that subject of review article.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include subtitles or related topics to further organize the content. The text of review articles might contain up to 5000 words (excluding Abstract, references list and Tables). Number of references list should not exceed 90.

3. Case Reports: Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens.

The manuscript should contain English abstract, a maximum of 250 words, but a structured abstract is not required. The main text should include titles or related topics to further organize the content. The manuscript could be of up to 2500 words (excluding references list and abstract) and could be supported with up to 25 references.

4. Editorial: Special articles are written by editor or editorial board members. An abstract is not usually included in editorials.

5. Letter to the Editor: These are letters which include different views, experiments and questions of the readers about the manuscript and should preferably be related to articles previously published in the Journal or views expressed in the journal. These should be short and decisive observations. They should not be preliminary observations that need a later paper for validation. The letter could have up to 1000 words and a maximum of 15 references.

Please contact the Editor at tip.dergi@mku.edu.tr for sending this type of papers.

Submission Files

This journal follows a double-blind reviewing procedure. Authors are therefore requested to submit a blinded manuscript, and a separate title page.

You may download blinded manuscript and title page templates by following the links on Journal's homepage.

a) Copyright and Ethical Declaration Form

b) Full Manuscript File: This is the blinded manuscript file that will be presented to the reviewers. The main text of the article, beginning from Abstract till references list (including tables, figures or diagrams) should be in this file. The file must not contain any mention of the authors' names or initials or the institution at which the study was done, ethical committee or acknowledgements. Manuscripts not in compliance with the Journal's blinding policy might be returned to the corresponding author. Please, use only Microsoft Word Document files. Do not zip the files. The name of the institution or hospital

xix

which will reveal the place where the study was conducted should be blinded as "... University" or "... Hospital".

The full manuscript file should not include the author information, email address of any authors, ORCID iDs, any disclaimers, sources of support, conflict of interest declaration, ethical committee, contact information of the corresponding author, and acknowledgement. This file will be shared with reviewers.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Information about the study design could be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Please avoid capitalizing all letters of the title and capitalize only the capital letter of first word of the title, proper nouns, proper adjectives. Other words and conjunctions (e.g., and, but, both, or, either, neither, nor, besides, however, nevertheless, otherwise, so, therefore, still, yet, though etc.) should be in small letters. No abbreviations or acronyms should be used within the titles.

Short title

You should add a running title not exceeding 40 characters to be placed at the header of the inner pages.

c) Title Page File: Only descriptive parts of the manuscript should be included in this file. General information about the article and authors is presented on the title page file and it should include the article title in English, author information, email address of each (all) author, ORCID iDs, any disclaimers, sources of support, conflict of interest declaration, ethical committee information, contact information of the corresponding author, acknowledgement and authorship contribution. This file will not be shared with reviewers.

Author information. Each author's highest academic degrees should be listed. The name of the department(s) and institution) or organizations where the work and email addresses should be attributed should be specified.

ORCID iD information of all authors is required by the TR Index.

Corresponding Author. One author should be designated as the corresponding author, and his or her email address should be included on the full manuscript file. This information will be published with the article if accepted. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Conflict of Interest declaration. A conflict of interest can occur when you (or your employer or sponsor) have a financial, commercial, legal, or professional relationship with other organizations, or with the people working with them, that could influence your research.

Some authors claim, the influence of the pharmaceutical industry on medical research has been a major cause for concern. In contrast to this viewpoint, some authors emphasize the importance of pharmaceutical industry-physician interactions for the development of novel treatments and argued that moral outrage over industry malfeasance had unjustifiably led many to overemphasize the problems created by financial conflicts of interest.

Thus, full disclosure is required when you submit your paper to the Journal. The journal editor will use this information to inform his or her editorial decisions and may publish such disclosures to assist readers in evaluating the article. The editor may decide not to publish your article based on any declared conflict. The conflict of interest should be declared on your full manuscript file or on the manuscript submission form in the journal's online peer-review system.

Sample personal statement for no conflict of interest:

On behalf of all authors, I, as the corresponding author, accept and declare that; we have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Sample personal statement for potential conflict of interest:

On behalf of all authors, I, as the corresponding author, accept and declare that; the authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

[Please specify name of the author(s) and nature of the conflict]

Acknowledgement

The Acknowledgements section immediately precedes the Reference list. All contributors who do not meet the criteria for authorship should be listed in an 'Acknowledgements' section. Additionally, if the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article in the Acknowledgements section. Authors should also disclose whether they had any writing assistance.

Authorship contribution: please indicate which part of the article each author contributed .

Article Format

The submitted file must be in Microsoft Word Document format.

The page size must be 210 mm × 297 mm (A4 size). All margins must be

set to 2.5 cm. If you are using Microsoft Word 2007 or later, you can easily set the margin by choosing "Normal" setting from Margins menu within Layout tab. The text layout should consist of single column.

Do not capitalize diseases or syndromes unless they include a name or proper noun. Note that the words "syndrome" and "disease" are never capitalized; for example, Down syndrome, Hodgkin disease.

The authors should turn off automatic hyphenation. Do not use hyphens with common prefixes unless the word looks confusing when closed up or unless the prefix precedes a proper noun, some other capitalized word, or an abbreviation. Common prefixes that should be "closed up" include ante, anti, hi, co, contra, counter, de, extra, infra, inter, intra, micro, mid, neo, non, over, post, pre, pro, pseudo, re, semi, sub, super, supra, trans, tri, ultra, un, and under.

Use italics sparingly for emphasis in the text.

Spell out Greek letters or use the "Insert, Symbol" feature in Microsoft Word. Do not create your own symbols.

Do not use italics for common expressions, such asin vivo, in utero, en face, aide-mémoire, or in situ.

Use bold type sparingly in text because it competes with headings for the reader's attention.

Always use numerals for statistics, ages, and measurements (including time, for example, 3 weeks). For other uses, spell out numbers from one to nine only.

Spell out abbreviations at first mention in the manuscript, with the abbreviation following in parentheses (except for units of measure, which are always abbreviated following numerals).

Manuscripts including tables, references list and figure legends, must be typewritten with a Unicode font (e.g., Times New Roman, Arial, etc.) that is available both for Windows and Mac Os operating systems. Please avoid using a mixture of fonts or non-Unicode fonts that do not support accented characters. The recommended font size is 12 points, but it may be adjusted for entries in a table. Authors should use true superscripts and subscripts and not "raised/lowered" characters. For symbols, please use the standard "Symbol" fonts on Windows or Macintosh.

Use the TAB key once for paragraph indents, not consecutive spaces. The pages should be numbered consecutively, beginning with the first page of the blinded article file. The pages should include title and abstract in English, the main text, tables, figures or diagrams-if exists- and reference list.

The title of the article should be centered at the top of the main text page, with the abstract below, and followed by Keywords. The capital letter of the first word of title should start with upper case letter. Please avoid capitalizing all letters of the title and conjunctions. The title, abstract, and keywords should be present in English and must be organized respectively. In order to start the Introduction section in a new page, a page break could be inserted at the end of Keywords.

While figure legends should be placed below the figures themselves, table captions should be placed above each table. Characters in figures, photographs, and tables should be uncapitalized in principal.

It would be appropriate to place the figures, tables and photographs at the end of the main text. Please, insert them at the end of main text at appropriate sizes, and order.

Figures and Figure Legends

Dear author, since the Journal has decision of publishing online, there is no need to upload the photos, pictures, drawings or shapes in the article as a separate file. However, to avoid blurring of images in the pdf of the article, you should add the photos or other images (X-ray, BT, MR etc.) in your Microsoft Word program as follows.

Insert menu - Pictures - Related image file in your computer

You must add the related image file on your computer and add the picture width to 16 cm. Since the need to upload each image (photo, X-ray, BT, MR or other images) is eliminated, please do not upload it to the system during submission. Place only at the end of full text and blind text.

The sections (i.e., Introduction, Method, Case, Results, Discussion, and Conclusion) and their subheadings should not be numbered. Paragraphs might be aligned left or justified, but this situation should be consistent throughout the article. Please, use single return after each paragraph. All headings should be typed on a separate line, not run in with the text. There should be no additional spacing before or after lines. Headings and subheadings should not be numbered, and their depth should not exceed three levels. You should not use the "Endnotes" or "Footnotes" feature for your references and remove any Word specific codes. When 'Magic Citations' inserts citations, or formats your manuscript in Microsoft Word, it uses "fields", which you can typically recognize as boxes that turn grey when the insertion point is placed inside one of them. Here is how to remove the fields in a Microsoft Word document:

1. Make a copy of the final manuscript. From the File menu in Word, select the Save As command. Give the file a new name.

2. In the new file, go to the Edit menu and choose Select All.

3. Press Ctrl+Shift+F9 or Cmd+6 to unlink all fields.

Your in-text citations and bibliography will become regular text, without field codes or any hidden links. If you want to do further editing or change citations in any way, make the changes to the original file. When you are ready to submit your manuscript, make another copy of the original file to unlink field codes.

xxi

Reviewer Guide

Dear Reviewer,

Thank you for agreeing to conduct a peer review which will help us decide whether a manuscript is to be published in this journal.

Peer-review is a critical part of the functioning of the scientific community, of quality control, and the self-corrective nature of science. Participating in peer review of scientific publications can be viewed as a responsibility, a burden, and an opportunity all at the same time. Nonetheless, peer review remains a critical component of our profession that helps to ensure the quality, originality, and reliability of scientific findings and claims. Peer review is requested of a colleague with specific interest and expertise in the topic relevant to the manuscript submitted to The Journal. Yet despite the importance of this process in upholding rigorous scientific standards and the integrity of the journal, few if any reviewers receive any formal training or instruction in how to provide a quality manuscript review. This document serves to orient and guide individuals asked to provide peer review for This journal in the process and responsibilities of review and reviewer. In doing so, the hope is to increase scientific quality of the manuscripts and contribution to the medical scientific community.

Process of peer review in The Journal

The journal utilizes a standard online site https://dergipark.org.tr), supported by TUBİTAK, for the process of both manuscript submission and manuscript peer review. Upon receiving a manuscript submitted for consideration of publication to The Journal, the Journal Manager and editorial staff review the submission to assure all required components as outlined in the Guide for Authors are included. The manuscript is then assigned to one of the Co-Editors (either the Editor in Chief or an Associate) Editor who directs and oversees the peer-review process. The Co-Editor then reviews the submission for relevance, content and quality. Those submissions deemed appropriate for consideration of publication are then assigned to at least two peer reviewers. Selection of these reviewers is a key step in the peer review process, as this represents a critical component in ensuring quality of manuscript review and in the overall quality of the Journal. Specifically, the selection of a reviewer with expertise in the topic of the manuscript to be reviewed and without any conflict of interest improves both the timeliness and quality of the review. As such, the designation of an area of interest or expertise by the reviewer (entered at the time of registration into the system (and updated in the change details section of the website, in the subsection areas of expertise) is critical for this component of the process. Reviews are chosen to a great extent from members of the advisory board.

Once the reviewers are selected by the editor, an email is sent requesting the review; 30 days is provided to choose to review (or not review) the manuscript. A lack of response to this request leads to the reviewer being uninvited. Statistics on individual reviewers are maintained and reviewed by the journal editors, including the number of reviews requested (and those accepted, uninvited, and refused). These data help in the process of evaluating the overall quality of a reviewer and are used in the selection of future editorial board members.Before Accepting

Please consider the following:

Does the article you are being asked to review match your expertise?

If you receive a manuscript that covers a topic that does not sufficiently match your area of expertise, please notify the editor as soon as possible. Please feel free to recommend alternate reviewer.

Do you have time to review the paper?

Finished reviews of an article should be completed within four weeks. If you do not think you can complete the review within this time frame, please let the editor know and if possible, suggest an alternate reviewer. If you have agreed to review a paper but will no longer be able to finish the work before the deadline, please contact the editor as soon as possible.

Are there any potential conflicts of interests?

While conflicts of interest will not disqualify you from reviewing the manuscript, it is important to disclose all conflicts of interest to the editors before reviewing. If you have any questions about potential conflicts of interests, please do not hesitate to contact the receiving editorial office.

Finally: Educate yourself on the peer review process through the international guides on how to conduct a good review

Some resources;

https://violentmetaphors.com/2013/12/13/how-to-become-good-at-peer-review-a-guide-for-young-scientists/

https://www.theguardian.com/higher-education-network/blog/2013/sep/27/peer-review-10-tips-research-paper

https://www.degruyter.com/document/doi/10.7556/jaoa.2013.070/html

https://scholar.google.com.tr/scholar?hl=tr&q=good+peer+review&btnG=&lr=

(https://www.google.com.tr/search?num=50&btnG=Ara&q=how+to+write+a+good+peer+review).

Respond to the invitation as soon as you can – delay in your decision slows down the review process, whether you agree to review or not.

General criteria for a peer review

There are a number of general criteria that make for a quality review of a scientific manuscript, and a number of responsibilities that come with being a peer reviewer that further enhances the review process.

The peer reviewer is responsible for critically reading and evaluating a manuscript in their specialty field, and then providing respectful, constructive,

xxii

and honest feedback to authors about their submission. It is appropriate for the Peer Reviewer to discuss the strengths and weaknesses of the article, ways to improve the strength and quality of the work, and evaluate the relevance and originality of the manuscript.

Timely – Given the time sensitive nature of many scientific manuscripts, the rapid return of a solicited peer review minimizes the timeline between submission and decision (which helps the authors with resubmission if the manuscript is rejected and helps the journal with a shorter time from submission to publication if accepted). Thus, the reviewer plays a very important role in ensuring expeditious dissemination of data. Peer reviews that cannot be completed on time should not be accepted by the reviewer; every effort should be made to complete those accepted within the time allotted for review.

Fair – A reviewer has a responsibility to both The Journal and the author to provide a review that is thoughtful and complete. While the immediate goal of peer review is providing a decision regarding the suitability for publication in the journal, an additional goal is to provide the author comments that will ultimately improve the science and manuscript and providing it the best chance for publication in a peer-reviewed journal. For manuscripts eventually accepted for publication, quality peer review will ensure that the highest quality science is ultimately published (and will weed out unsound papers). Peer reviews requested in areas outside of the area of expertise of a reviewer should not be accepted; in that case, the review process is facilitated by the reviewer recommending those who could provide a quality review.

Collegial – It is rare for any manuscript to be reviewed without comments or criticisms. However, the responsibility of the reviewers is to provide these critiques constructively and objectively, and in a fashion, that is collegial and respectful. Consider each manuscript as one that was written by a valued colleague when drafting a peer review. Importantly, review the manuscript as you would like your own manuscript reviewed.

Clear – The goal of peer review is to provide an advisory recommendation to the editors as to the suitability of a manuscript for publication in The Journal. As such, the responsibility of the reviewer is to provide a clear signal to the editor regarding the appropriateness and priority for publication of a manuscript. The reviewer is expected to provide comments and criticisms to the editor that clearly justifies their recommendation for disposition of the manuscript. It is also critical that the comments to the editor are consistent with those made to the author (such that the comments of the reviewer justify the recommendation regarding the disposition of the manuscript).

Comprehensive – A quality review will include a number of considerations, and may be specific to the manuscript being reviewed. In order for a manuscript to be considered for publication, it must be original and significant, providing a contribution to research and importance to field. In general, there should be no flaws in the specific procedures used in performance of the study, or in the logic used for the interpretation of the data. It is important that the results of the study support its conclusions, and that there are no errors in reference to prior work (or no exclusions of pertinent references). Where appropriate, confirmation of regulatory review (such as institutional review board approval) must be present. A reviewer is expected to comment on the strengths and weaknesses or limitations of the study. The validity of the statistics used (often including a justification of a sample size) to analyze data is necessary, and the data presented in the figures and tables should be reflective of the results presented and adequate to justify the study conclusions. In general, the manuscript length and quality of the writing are important to ensure its quality.

Considerations for a quality peer review of a manuscript

Structure

Is the article clearly laid out? Are all the key elements present: abstract, introduction, methodology, results, conclusions?

Consider each element in turn:

Title: Does it clearly describe the article? This will be used for medical database searches, so it shouldn't try to be "cute".

Abstract: Does it reflect the content of the article? Are the data consistent with the results reported in the manuscript?

Introduction: Does it describe what the author hoped to achieve accurately, and clearly state the problem being investigated? Normally, the introduction is two or three paragraphs long. It should summarize relevant research to provide context, and explain what findings of others, if any, are being challenged or extended. It should describe the experiment, hypothesis; general experimental design or method.

Methodology: Does the author accurately explain how the data were collected? Is the design suitable for answering the question posed? Is there sufficient information present for you to replicate the research? Does the article identify the procedures followed? Are these ordered in a meaningful way? If the methods are new, are they explained in detail? Was the sampling appropriate? Have the equipment and materials been adequately described? Does the article make it clear what type of data was recorded; has the author been precise in describing measurements?

Results: This is where the author should explain in words, tables and figures what was discovered in the research. It should be clearly laid out and in a logical sequence. You will need to consider if the appropriate analysis been conducted. Are the statistics correct? If you are not comfortable with statistics, advise the editor when you submit your report and recommend review by a statistical editor. Any interpretation should not be included in this section.

Conclusion/Discussion: Are the claims in this section supported by the results, do they seem reasonable? Have the authors indicated how the results relate to expectations and to earlier research? Does the article support or contradict previous theories? Does the conclusion explain how the research has moved the body of scientific knowledge forward?

xxiii

Language: If an article is poorly written due to grammatical errors, while it may make it more difficult to understand the science, you do not need to correct the language. You may wish to bring it to the attention of the editor, however, and we can refer the authors to an language editing service if you feel the paper may be worth publishing.

Finally, on balance, when considering the whole article, do the figures and tables inform the reader, are they an important part of the story? Do the figures describe the data accurately? Are they consistent (are the bars in the charts the same width, are the scales on the axis logical)? Are the legends appropriate?

Previous Research

If the article builds upon previous research, does it reference that work appropriately? Are there any important works that have been omitted? Are the references accurate and up to date?

Reviewer's Suggestions

Once accepted, the reviewer has 4 weeks to complete the review (details of the components of a review are described in more detail below), which is submitted through The Journal site. Failure to complete the review during this time period leads to a reminder email.

It is the responsibility of the reviewer to provide a recommendation to the editor for the disposition of the manuscript. Importantly, the recommendation of the reviewer is advisory to the editor, as it is ultimately the decision of the editor as to the final disposition of the manuscript.

When the editor has a full complement of reviews completed, the editor reviews the comments and recommendations, and a decision regarding the suitability for publication of the manuscript is made.

The recommendations can be categorized into 6 groups.

Accept Submission (without modification)

Minor Revision (Revisions Required): Accept with minor modification (but manuscript requires modifications to improve its quality)

Major Revision (Resubmit for Review): Major modifications required, manuscript is unique, but requires extensive revision and reevaluation prior to potential acceptance

Resubmit Elsewhere: manuscript is unique, but out of the journal scope.

Decline Submission: manuscript is of low quality or low interest to the readership)

The reviewer has two types of comments that can be provided – one to the authors, and one to the editors. It is strongly encouraged that the reviewer utilizes the comments to the editor to provide confidential comments regarding the manuscript under consideration. These comments help assure that the editor understands the true recommendation of the reviewer and provides key assistance to the Editor in determining a manuscript's ultimate disposition. In addition, completing the manuscript rating form is helpful in supporting a reviewer's recommendation for the disposition of a manuscript, and assists the Editor in justifying the final decision.

Review of the reviewer

The editor evaluates the quality of a review upon its receipt. Utilizing the criteria defining a quality review (timely, fair, collegial, clear, and comprehensive), a reviewer is evaluated and scored (from 0-5) on their review. This statistic, in combination with a separate statistic regarding the timeliness of the review, is helpful in assigning subsequent reviews to a reviewer. Reviewers with low scoring or late reviews are not considered highly for subsequent reviews.

Why be a reviewer?

Reviewing requires the investment of time and a certain skillset. Before you decide if you want to become a reviewer, we recommend that you read more about the peer review process and conducting a review.

A reviewer may directly benefit from the peer review process by learning from the work of others prior to publication. Reviewer's insights may also lead to future research ideas, improvements in their own study design and manuscript preparation. In addition, The Council of Higher education supports peer reviewing financially within the context of academic refunds.

As a reviewer, you can;

Establish your expertise in the field and expand your knowledge.

Improve your reputation and increase your exposure to key figures in the field.

Stay up to date with the latest literature, and have advanced access to research results.

Develop critical thinking skills essential to research.

Advance in your career – peer review is an essential role for researchers.

Important Considerations;

* It is important for our Journal that you ***request a revision*** by making criticism, evaluation and comments that will help to enrich the scientific content of the article.

* You can **suggest rejection for outdated or inadequate studies** that are similar to previous studies but do not have significant scientific value, or contain some fundamental mistakes or erroneous judgments.

* In accordance with the TR Index criteria, in all (research) studies that require ethics committee approval, a legible copy of the ethics committee approval is required to be uploaded to the system together with the article files, and the manuscript is not sent to our reviewers for evaluation before this process is fulfilled.

xxiv

* In accordance with the principles of double-blind review, the information regarding the approval of the center where the study was conducted and the approval of the ethics committee were removed from the article after we reviewed it and will be added again during the copyediting following the end of the review. There is no need for our reviewers to make an examination in this respect.

* Before all studies are sent to the reviewer, while they are in the pre-control stage, they are subjected to "Similarity Check" with iThenticate Crosscheck software and if they are above the tolerable level, the author is requested to make the necessary corrections.

* We ask the authors to use a dot as a decimal separator throughout the article, including the Turkish and English abstracts, so this is not an error.

* Therefore, we would like to inform you that there is **no need for you to request any correction regarding the use of a dot as a decimal separator or not, whether the approval of the ethics committee** has been obtained.

Ethical Principles and Editorial Policy

Ethical Responsibilities of The Editors

The Journal is committed to practice the publication ethics and takes all possible measures against any publication malpractices.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of The International Council of Medical Journal Editors (ICMJE), The World Association of Medical Editors (WAME), The Council of Science Editors (CSE), The Committee on Publication Ethics (COPE), The European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (https://doaj.org/bestpractice).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

The Journal requires corresponding authors to submit a signed and scanned version of the Copyrights & Ethics form (available for download through this link) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all responsibility for authorship during the submission and review stages of the manuscript.

The Journal requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interest, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complain t cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to cases that cannot be resolved internally. The Editor-in-Chief is the final authority in the decision- making process for all appeals and complaints.

The Journal is committed to objective and fair double-blind peer-review of the submitted for publication works and to prevent any actual or potential conflict of interests between the editorial and review personnel and the reviewed material. Details on this subject have been explained in the authors guide and reviewers guide respectively.

Ethical Responsibilities of The Authors

Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts submitted to another journal for evaluation but rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Individuals listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org).

The ICMJE recommends that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;

2. Drafting the work or revising it critically for valuable intellectual content;

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for

XXV

other specific parts of the work. Besides, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged on the title page of the manuscript.

When submitting a manuscript to The Journal, authors agree to assign the copyright of their manuscript to the Journal. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. The Journal requires each submission to be accompanied by a Copyright and Ethical Form (available for download at Journal Website). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial, and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in The Journal reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; thus, the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility regarding the published content rests with the authors.

To summarize, all authors submitting their works to the journal for publication as original articles attest that the submitted works represent their authors' contributions and have not been copied or plagiarized in whole or in part from other works. The authors acknowledge that they have disclosed all and any actual or potential conflicts of interest with their work or partial benefits associated with it.

Ethical Responsibilities of The Reviewer

Given the sensitive nature of peer review, there are ethical responsibilities of the review and review process that are critical to ensure their validity. It is important for reviewers to identify potential conflicts of interest with the authors and the topic of the manuscript. The Journal requires that reviewers disclose potential and relevant conflicts of interest related to employment, consultancies, stock ownership, receipt of honoraria, patents, a professional relationship with, or direct competition in the field of the authors. The reviewer has a responsibility to review the conflict-of-interest forms submitted by the authors, which specifically document any relevant financial relationships.

Given the role of reviewer as an expert in the topic area of the manuscript, a reviewer is requested to report any known situations of duplicate submissions (a manuscript that may be under concurrent review at another journal), fraudulent data, or plagiarism in a manuscript. If identified, these comments should be conveyed to the editor (in the confidential comments to the editor section) so they can be addressed as appropriate. Since peer review of a manuscript allows a reviewer to view data that is not yet in the public domain, strict confidentiality is critical to ensure scientific integrity; destruction of documents and files related to peer review is also mandatory once the review is complete.

The Committee on Publication Ethics (COPE) is a group comprised of editors of academic journals and others interested in publication ethics. Members of COPE were provided with the Ethical Guidelines for Peer Review, describing the basic principles to which reviewers should adhere. These guidelines provide a broad ethical context in which the peer review process should be performed.

COPE Ethical Guidelines for Peer Reviewers

Peer review in all its form plays an important role in ensuring the integrity of the scholarly record. The process depends to a large extent on trust and requires that everyone involved behaves responsibly and ethically. Peer reviewers play a central and critical part in the peer-review process, but too often come to the role without any guidance and may be unaware of their ethical obligations. The COPE Ethical Guidelines for Peer Reviewers set out the basic principles and standards to which all peer reviewers should adhere during the peer-review process. It is hoped they will provide helpful guidance to researchers, be a reference for journals and editors in guiding their reviewers, and act as an educational resource for institutions in training their students and researchers.

Basic principles to which peer reviewers should adhere

Peer reviewers should:

• only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner

• respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal

• not use information obtained during the peer-review process for their own or any other person's or organization's advantage, or to disadvantage or discredit others

• declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest

• not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations

• be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments

• acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner

• provide journals with personal and professional information that is accurate and a true representation of their expertise

• recognize that impersonation of another individual during the review process is considered serious misconduct

xxvi

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2025;16(54)

CONTENTS

Volume: 16, Issue 54, Year: April 2025

xxvii

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1547490
Interdiscip Med J 2025;16(54):1-7

The role of erythrocyte distribution width, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in the development of graft rejection after keratoplasty

Mustafa Yıldırım **Büşra Çalışkan** **İbrahim Koçer**

Ataturk University Faculty of Medicine Department of Ophthalmology, Erzurum, Türkiye

Abstract

Objective: The aim of this research is to evaluate the pre-surgical Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Red Cell Distribution Width (RDW) in patients undergoing rekeratoplasty compared to control subjects.

Method: Penetrating keratoplasty (PKP) cases performed between 2013 and 2023 were evaluated retrospectively. The follow-up period was determined as at least 6 months. The first group consisted of 31 patients who underwent rekeratoplasty due to corneal graft rejection after PKP, and the second group consisted of 31 patients with the same diagnosis who did not experience graft rejection during their follow-up after PKP. NLR, PLR and RDW values from the preoperative complete blood count results of all patients were included in the study.

Results: Upon demographic analysis, it was evident that although no notable age discrepancy existed between the two categories, the prevalence of rekeratoplasty was considerably higher in males. Primary diagnoses of the disease did not appear to have a significant impact on the risk of rejection. There was no observable correlation between serum NLR, PLR and RDW levels and graft rejection. Nevertheless, a notable association was detected between RDW and the duration until the occurrence of the initial rejection episode.

Conclusion: High RDW value, which is an indicator of systemic inflammatory state, was found to be associated with the time to first rejection reaction in corneal transplant patients and graft rejection patients compared to controls, as in many diseases. RDW in terms of rejection reaction risk prediction and prognosis; it can be used as a useful, cheap and practical parameter.

Keywords: Penetrating keratoplasty, graft rejection, NLR, PLR, RDW.

INTRODUCTION

Penetrating keratoplasty (PKP) is a surgical procedure in which the diseased cornea of a patient is replaced with healthy, transparent corneal tissue obtained from a deceased donor. Corneal transplantation is considered the most successful type of allograft transplantation in humans in terms of outcomes (1). While it was traditionally performed as a penetrating (full-thickness) procedure for many years, advancements in surgical techniques have led to the development of lamellar keratoplasty methods. These novel techniques, tailored to the specific diagnosis, have significantly reduced the risk of tissue rejection (2,3). Nevertheless, PKP remains the first choice, particularly in conditions such as advanced keratoconus, keratitis sequelae, and bullous keratopathy.

Corneal transplantation differs from other organ transplants, such as liver, heart, and kidney transplants, because it does not rely on compatibility with major histocompatibility complex (MHC) class antigens (4). Consequently, the use of systemic immunosuppressive agents is not required. However, immune-mediated graft rejection remains one of the most significant causes of corneal graft failure.

Penetrating keratoplasty-related risk factors have been

Cite this article: Yıldırım M, Çalışkan B, Koçer İ. The role of erythrocyte distribution width, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in the development of graft rejection after keratoplasty. Interdiscip Med J. 2025;16(54):1-7 https://doi.org/10.17944/interdiscip.1547490

Corresponding Author: Dr. Mustafa Yıldırım, Ataturk University Faculty of Medicine, Department of Ophthalmology, Erzurum, Türkiye
E mail: mustafa.yildirim@atauni.edu.tr
ORCID iD: 0000-0002-2706-3592

Received: Sep 11, 2024
Accepted: Dec 6, 2024

identified in the literatüre (3-6). Loss of corneal transparency and potential graft rejection can arise from various factors leading to local inflammation and vascularization in the graft tissue. Prolonged graft survival is noted, particularly in conditions like bullous keratopathy and keratoconus, where inflammation is less pronounced. The literature indicates that the occurrence of graft rejection following PKP varies between 4% and 20% (3).

The total count of white blood cells and their subtypes, as well as their rates (Neutrophil-to-lymphocyte ratio; NLR, platelet-to-lymphocyte ratio; PLR), are increasingly being used to indicate chronic inflammation (7-9). Neutrophils become activated during tissue damage and release enzymes like myeloperoxidase, acid phosphatase, and elastase. When inflammation occurs, the proportion of circulating leukocytes changes, often leading to neutrophilia and relative lymphopenia. Existing literature suggests that NLR and PLR play a significant prognostic role in hypertension, hepatic cirrhosis, diabetes mellitus, familial Mediterranean fever, cardiovascular diseases, and malignancies (10).

Erythrocyte distribution width (RDW) is a commonly used laboratory parameter to assess erythrocyte anisocytosis, which reflects the variation in the size of circulating red blood cells (11). Initially, RDW was primarily utilized in clinical applications to distinguish between different types of anemias. However, in numerous recent publications, an increase in RDW has been associated with various diseases such as vascular occlusive disease, heart failure, hypertension, ischemic heart disease, the active stage of inflammatory bowel disease, atherosclerosis, rheumatoid arthritis, and other conditions linked to progressive inflammation (12-16). Several studies have stated that inflammation and oxidative stress impact RDW (15). Furthermore, RDW has been shown to be indicative of elevated levels of hepcidin, IL-6, TNF-alpha, and other circulating cytokines in the bloodstream (11).

The aim of this study was to evaluate the preoperative NLR, PLR, and RDW rates of patients undergoing rekeratoplasty compared to control subjects. Additionally, it was also aimed to investigate the potential of these parameters as markers of inflammation and predictors of graft rejection in the process leading to rekeratoplasty.

METHOD

Ethics committee approval was received from Atatürk University Faculty of Medicine Ethics Committee (B.30.2.ATA.0.01.00/40). The study was retrospectively designed with scanned patient files. The ethics committee did not request a patient consent form for the study. In the study, the files of patients who underwent rekeratoplasty surgery between 2013 and 2023 were scanned in 2 months. All authors had access to information that could identify individual participants at or after data collection.

The files of patients who underwent penetrating keratoplasty and had a follow-up period of at least 6 months were retrospectively reviewed. The data of patients who underwent rekeratoplasty between April 2013 and May 2023 were reviewed between January 2024 and March 2024. All individuals who underwent PKP were screened and those who underwent rekeratoplasty were identified from this group. Patients' medical records were reviewed for age, gender, primary indication for PKP, follow-up period, and timing of first detection of symptoms associated with graft rejection.

The first group consisted of 31 patients who underwent rekeratoplasty due to corneal graft rejection after PKP, and the second group consisted of 31 patients with the same diagnosis who did not experience graft rejection during their follow-up after PKP. The primary surgical indications for rekeratoplasty were bullous keratopathy, keratoconus, and nonspecific vascularized scar (leucoma).

The same treatment protocol was applied to all patients. Following surgery, all patients received topical prednisolone, moxifloxacin, and autologous serum. Topical treatment was started immediately after surgery with all drops applied five times daily, antibiotic drops were discontinued at month 1, steroid drops were tapered to three times daily at month 3, twice daily at month 6, and once daily at month 12. Artificial tear drops were continued five times daily for at least 1 year. Corneal sutures were generally removed 12 months post-surgery. The corneal graft rejection was diagnosed based on characteristic findings during slit lamp biomicroscopy, such as hyperemia, rejection line, infiltrations, keratic precipitates, and graft edema.

The time frame for the initial identification of symptoms of graft rejection after undergoing PKP surgery was determined for the patients in the first group. The preoperative complete blood counts of all patients were recorded including NLR, PLR, and RDW values. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, and PLR by dividing the number of platelets by the number of lymphocytes.

The aim was to analyze the relationship between the systemic inflammation-related values and the timing of occurrence graft rejection following keratoplasty. Participants with preoperative glaucoma, endophthalmitis, inflammatory ocular diseases like severe dry eye and atopic keratoconjunctivitis, as well as those with a history of systemic infectious and inflammatory diseases, were excluded from the study.

RESULTS

The study consisted of a total of 62 participants, 31 patients who underwent re-keratoplasty formed the experimental group while the control group consisted of 31 patients who did not experience rejection after keratoplasty. The time from the first surgery to the first appearance of graft rejection symptoms in rekeratoplasty patients was calculated. The preoperative neutrophil (NE), lymphocyte (LY), platelet (PLT), NLR, PLR, and RDW values for all patients were determined.

The demographic data and the average NE, LY, PLT, RDW, NLR, and PLR values of the patients assessed before the operation are outlined in Table 1.

Table 1. The demographic and average hematological data of the patients

	Mean	Standard deviation	Median
Neutrophil	4.66	1.43	4.46
Lymphocyte	2.46	0.77	2.37
Erythrocyte distribution width	13.4	1.4	13.0
Platelet	265	65	268
Neutrophil-to-lymphocyte ratio	2.04	0.80	1.99
Platelet-to-Lymphocyte ratio	117.06	44.32	109.80
Age	53	19	54
The first rejection time (months)	38	32	32
Sex	Count	%	
Male	38	61.3%	
Female	24	38.7%	

The average ages of both groups were similar, but there was a significantly higher incidence of rekeratoplasty among male participants in the experimental group (p=0.01) (Table 2, Figure 1).

Table 2. Survival rate by gender

Case processing summary

Sex	Total Count	Count of events	Censored	
			Count	%
Male	38	24	14	36.8
Female	24	7	17	70.8
Overall	62	31	31	50.0

The NLR, PLR, and RDW values did not show any significant difference related to rejection risk. The mean survival time of the grafts was 62 months. Male patients developed rejection after an average of 49.339 months, while this period for female patients was an average of 60.602 months, and a statistically significant difference was detected between the two groups (p = 0.011) (Table 3).

There was no significant difference found when the diagnostic groups were compared in terms of their progression to rejection reaction and survival time (p= 0.907) (Table 4, Table 5, Figure 2).

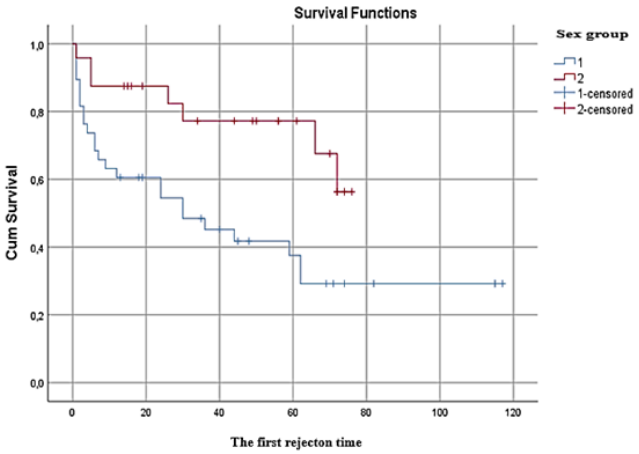

Figure 1. Survival rate by gender

Table 3. Means and medians of survival time by sex

Sex	Mean*				Median			
	Estimate	SE	95% CI		Esti-mate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Male	49.339	8.139	33.387	65.291	30.000	14.187	2.193	57.807
Female	60.602	5.493	49.835	71.369				
Overall	62.233	6.701	49.099	75.368	62.000	13.295	35.942	88.058

*Estimation is limited to the largest survival time if it is censored; SE, Standard error,; CI, Confidence interval

Table 4. Case processing summary

Diagnostic groups	Total count	Count of events	Censored	
			Count	%
Leucoma	34	17	17	50.0
Keratoconus	12	6	6	50.0
Bullous keratopathy	16	8	8	50.0
Overall	62	31	31	50.0

Table 5. Means and medians of survival by diagnosis

Diagnostic groups	Mean*				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Leucoma	64.062	9.088	46.249	81.876	72.000	30.537	12.148	131.852
Keratoconus	49.488	9.658	30.558	68.419	62.000	21.877	19.122	104.878
Bullous keratopathy	43.083	7.261	28.852	57.315	62.000	23.787	15.377	108.623
Overall	62.233	6.701	49.099	75.368	62.000	13.295	35.942	88.058

*Estimation is limited to the largest survival time if it is censored; SE, Standard error

The preoperative average NLR, PLR, and RDW measurements were analyzed for the patients. No significant correlation was observed between NLR (p=0.074) and PLR (p=0.111) values and the first rejection time (p> 0.05).

A significant result was found between RDW values and first rejection time. Patients with a RDW value greater than 13.431 have a 1.38-fold higher likelihood of experiencing rejection compared to those with a value below this threshold. The result is statistically significant (p=0.012) (Table 6).

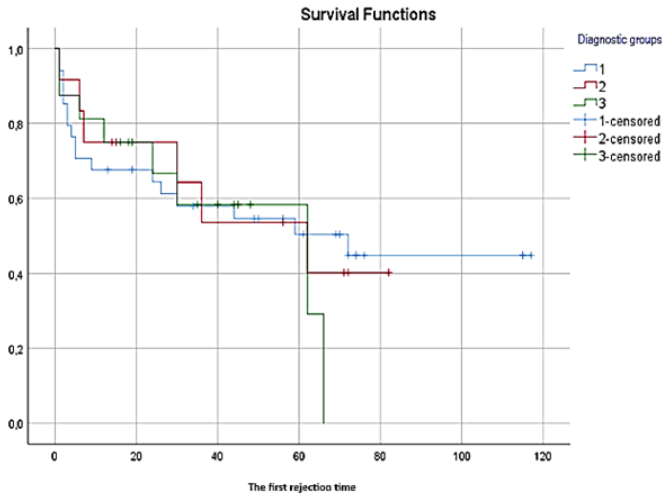

Figure 2. Survival rate by diagnostic groups

In individuals experiencing corneal transplant rejection and subsequent repeat corneal transplant surgery, an assessment was conducted on systemic inflammatory markers. The potential utilization of these markers as predictive indicators for assessing the risk in patients undergoing penetrating keratoplasty (PKP) was explored.

For this purpose, the retrospective analysis examined the demographic characteristics, primary indications, and preoperative systemic inflammatory indicators of patients who experienced graft rejection post- PKP and subsequently underwent rekeratoplasty. It also considered a control group of patients with a similar PKP diagnosis who did not experience graft rejection. NLR, PLR, and RDW values were assessed. The time taken for the first signs of graft rejection to appear after the initial surgery was calculated for the rekeratoplasty patients.

Upon demographic analysis, it was evident that although no notable age discrepancy existed between the two categories, the prevalence of rekeratoplasty was considerably higher in males.

Table 6. Variables in the equation

	Mean	B	SE	p	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
RDW	13.431	0.324	0.129	0.012	1.383	1.075	1.780
NLR	2.037	0.434	0.243	0.074	1.544	0.959	2.485
PLR	117.058	-0.010	0.006	0.111	0.990	0.978	1.002

RDW, Erythrocyte distribution width; NLR, Neutrophil-to-Lymphocyte ratio; PLR: Platelet-to-Lymphocyte ratio, SE, Standard error

The main indications for primary keratoplasty were leukoma, bullous keratopathy, and keratoconus. It has been noted that the primary diagnoses of the condition did not show a substantial impact on the risk of rejection.

There was no observable correlation between serum NLR, PLR and RDW levels and graft rejection. Nevertheless, a notable association was detected between RDW and the duration until the occurrence of the initial rejection episode.

DISCUSSION

PKP is a crucial surgical procedure for treating corneal diseases or preventing vision loss. While visual complaints constitute an indication in most cases, it is also applied for therapeutic and/or tectonic purposes.

Advances in corneal transplant surgery and the increased availability of donor material have led to a rise in primary PKPs. Consequently, there has been an increase in rekeratoplasty procedures and graft failure has become a common cause of transplantation (17).

Recently, NLR, PLR, and RDW values are now accepted as simple markers for systemic inflammation. In some studies, NLR and PLR have been identified as prognostic markers in hypertension, diabetes mellitus, familial Mediterranean fever, cardiovascular diseases, hepatic cirrhosis, and malignancies (10). Moreover, several studies have highlighted the potential of RDW as an inflammation marker and showing its increase during inflammatory processes. In these studies, RDW was stated to be a prognostic factor in conditions such as stroke,

myocardial infarction, sepsis, and cancer (18,19).

The level of these inflammatory parameters has been studied in various eye diseases. Ozkok et al. investigated the relation between RDW values and visual potential in retinal vein occlusion (RVO), and they found a significant elevation in RVO cases compared to the control group. Higher RDW level was associated with lower best corrected visual acuity (20). Yingbo et al. examined the correlation between RDW and diabetic retinopathy (DRP), revealing a heightened incidence of DRP in diabetic patients with high RDW (21). Similarly, Pinna et al. found a substantial association between elevated RDW levels and non-arteritic anterior ischemic optic neuropathy (22).

Elbeyli et al. assessed RDW, PLR, and NLR parameters in patients with central retinal artery occlusion (CRAO), indicating that RDW seemed to outperform other inflammatory indices in predicting CRAO (23). In a study on PKP, Yıldız et al. evaluated systemic inflammatory parameters in patients who developed corneal graft rejection after PKP and found the NLR rate to be low in these patients (24).

In this study, in patients who had corneal graft rejection after PKP and underwent rekeratoplasty; systemic inflammatory parameters were evaluated. The usability of these parameters as prognosis indicators in PKP patients in terms of risk prediction was investigated. In terms of rekeratoplasty, no significant relationship was found between serum NLR, PLR, and RDW values and graft rejection. Again, it was observed that the primary diagnoses did not make a significant difference in terms of keratoplasty indications. The absence of difference in the keratoconus group, which has a low expected risk of graft rejection, may be attributed to the exclusion of patients who underwent DALK (deep anterior lamellar keratoplasty) from the study. While there was no demographic difference in age between the two groups in the study, it was observed that the rekeratoplasty rate was significantly higher in the male gender. This situation may be related to differences in the patients' immune systems. It also suggests that there may be differences between genders in terms of adherence to follow-up and treatment.

Limitations of the Study

The study has some limitations. Only PKP cases were included in the study and the number of cases was limited. Today, the preference of lamellar keratoplasty instead of PKP according to indication and the reduce in rejection rates have limited the number of patients. Due to the nature of the study, RDW values could not be evaluated during the period when the rejection reaction occurred and during follow-ups.

CONCLUSION

In conclusion, high RDW value, which is an indicator of systemic inflammatory state, was found to be associated with the time to first rejection reaction in corneal transplant patients and graft rejection patients compared to controls, as in many diseases. As far as is known, this is the first study investigating the relationship between the duration of graft rejection and RDW in corneal transplant patients. RDW, in terms of rejection reaction risk prediction and prognosis; can be used as a useful, cheap, and practical parameter. In order to better understand the role of these hematological parameters in graft rejection, comprehensive studies that include lamellar keratoplasties in addition to PKP are needed.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: Ethical permission was obtained from the Ataturk University Non-interventional ethics committee for this study with date February 21, 2024 and number B.30.2.ATA.0.01.00/40 and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions: Concept: MY, BÇ, Design: MY, BÇ, Supervising: MY, İK, Financing and equipment: NONE, Data collection and entry: BÇ,MY, Analysis and interpretation: MY, İK, Literature search: BÇ, Writing: BÇ,MY, Critical review: İK

REFERENCES

1. Gain P, Jullienne R, He Z, et al. Global survey of corneal transplantation and eye banking. JAMA Ophthalmol 2016;134(2):167–73. https://doi.org/10.1001/jamaophthalmol.2015.4776
2. Akanda ZZ, Naeem A, Russell E, Belrose J, Si FF, Hodge WG. Graft rejection rate and graft failure rate of penetrating keratoplasty (PKP) vs lamellar procedures: a systematic review. PLoS ONE 2015;10(3):e0119934. 2. https://doi.org/10.1371/journal.pone.0119934
3. Hos D, Matthaei M, Bock F, et al. Immune reactions after modern lamellar (DALK, DSAEK, DMEK) versus conventional penetrating corneal transplantation. Prog Retin Eye Res 2019; 73:100768. https://doi.org/10.1016/j.preteyeres.2019.07.001

4. Kumar V, Kumar A. Immunological aspects of corneal transplant. Immunol Invest 2014;43(8):888–901. https://doi.org/10.3109/08820139.2014.910024

5. Niederkorn JY, Larkin DF. Immune privilege of corneal allografts. Ocul Immunol Inflamm 2010;18(3):162–171. https://doi.org/10.1097/00007890-199906270-00001

6. Maguire M G, Stark, WJ, Gottsch, JD, Stulting RD, Sugar A, Fink NE. Collaborative Corneal Transplantation Studies Research Group. Risk factors for corneal graft failure and rejection in the collaborative corneal transplantation studies. Collaborative corneal transplantation studies research group. Ophthalmology 1994;101: 1536–1547.

7. Kim HS, Jung J, Dong SH, Kim SH, Jung SY, Yeo SG. Association Between High Neutrophil to Lymphocyte Ratio and Delayed Recovery From Bell's Palsy. Clin Exp Otorhinolaryngol. 2018;12(3):261-6. https://doi.org/10.21053/ceo.2018.01018

8. Mochimaru T, Ueda S, Suzuki Y, Asano K, Fukunaga K. Neutrophil to lymphocyte ratio is a novel independent predictor of severe exacerbation in asthma patients. Ann Allergy Asthma Immunol. 2019; 122(3):337-339.e1. https://doi.org/10.1016/j.anai.2018.11.029.

9. Hasselbalch, I. C., Søndergaard, H. B., Koch-Henriksen, N., et al. Th e neutrophil-to-lymphocyte ratio is associated with multiple sclerosis. Mult Scler J Exp Transl Clin. 2018; 28:4:2055217318813183. https://doi.org/10.1177/2055217318813183

10. Kara A, Guven M, Yilmaz MS, Demir D, Elden H. Are neutrophil, platelet and eosinophil-to-lymphocyte ratio and red blood cell distribution width can be used for nasal polyposis? Eur Arch Otorhinolaryngol. 2018;275(2):409-13. https://doi.org/10.1007/s00405-017-4821-3

11. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158(4):659-66. https://doi.org/ 10.1016/j.ahj.2009.07.024

12. Gunebakmaz, O., Kaya, M. G., Duran, M., Akpek, M., Elcik, D., Eryol, N. K. Red blood cell distribution width in 'non-dippers' versus 'dippers'. Cardiology 2012;123(3), 154-59. https://doi.org/10.1159/000342667

13. Nishizaki, Y., Yamagami, S., Suzuki, H., et al. Red blood cell distribution width as an effective tool for detecting fatal heart failure in super-elderly patients. Intern Med 2012;51(17):2271-6. https://doi.org/10.2169/internalmedicine.51.7938

14. Karabulut A, Uzunlar B. Correlation between red cell distribution width and coronary ectasia in the acute myocardial infarction. Clin Appl Thromb Hemost 2012;18(5):551-2. https://doi.org/10.1177/1076029611436198

15. Yeşil A, Şenateş E, Erdem ED, Demirtunç R, Övünç AOK. Red cell distribution width: a novel marker of activity in inflammatory bowel disease. Gut and Liver 2011;5(4):460-7. https://doi.org/10.5009/gnl.2011.5.4.460

16. Lee WS, Kim TY. Relation between red blood cell distribution width and inflammatory biomarkers in rheumatoid arthritis. Arch Pathol Lab Med 2010;134(4):505-6. https://doi.org/10.5858/134.4.505.c

17. Patel NP, Kim T, Rapuano CJ, Cohen EJ, Laibson PR. Indications for and outcomes of repeat penetrating keratoplasty, 1989–1995. Ophthalmology. 2000;107(4):719-24. https://doi.org/10.1016/s0161-6420(00)00003-8

18. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci. 2015;52(2):86-105. https://doi.org/10.3109/10408363.2014.992064

19. Esmaili HA, Taghipour H, Saburi E. Determining the Association between RDW and Traditional Markers of Inflammation. Annual Research & Review in Biology 2014;4(15): 2547-52. https://doi.org/10.9734/ARRB/2014/9651

20. Ozkok A, Nesmith BLW, Schaal S. Association of Red Cell Distribution Width Values with Vision Potential in Retinal Vein Occlusion. Ophthalmol Retina. 2018;2(6):582-6. https://doi.org/10.1016/j.oret.2017.09.018

21. Yingbo Ma, Li S, Zhang A, et al. Association between Red Blood Cell Distribution Width and Diabetic Retinopathy: A 5-Year Retrospective Case-Control Study. J Ophthalmol 2021;6653969. https://doi.org/10.1155/2021/6653969

22. Pinna A, Carlino P, Serra R, et al. Red Cell Distribution Width (RDW) and Complete Blood Cell Count-Derived Measures in Non-Arteritic Anterior Ischemic Optic Neuropathy. Int J Med Sci. 2021;18(10):2239-44. https://doi.org/10.7150/ijms.53668

23. Elbeyli A, Kurtul BE, Ozcan DO, Ozcan SC, Dogan E. Assessment of Red Cell Distribution Width, Platelet/

lymphocyte Ratio, Systemic Immune-inflammation Index, and Neutrophil/lymphocyte Ratio Values in Patients with Central Retinal Artery Occlusion. Ocul Immunol Inflamm. 2022;30(7-8):1940-4. https://doi.org/10.1080/09273948.2021.1976219

24. Yıldız MB, Yıldız E. Evaluation of serum neutrophil-to-lymphocyte ratio in corneal graft rejection after low-risk penetrating keratoplasty. Int Ophthalmol 2022;42(1):57-63. https://doi.org/10.1007/s10792-021-01999-4

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1541885
Interdiscip Med J 2025;16(54):8-17

The mediator role of alexithymia between childhood traumas and fibromyalgia impact level of patients with fibromyalgia

Mert Can Çoban, Haydeh Faraji

Istanbul Aydin University, Faculty of Science and Literature, Department of Psychology, Istanbul, Türkiye

Abstract

Objective: Fibromyalgia is a disease that is associated with childhood traumas. The person's alexithymic features, such as avoidance of intensely experienced negative emotions or the inability to express their emotions, may cause physical symptoms, particularly fibromyalgia. This study aimed to examine the relationship between fibromyalgia and childhood traumas and alexithymia.

Methods: Sample selection was made using the convenience sampling method. A total of 185 patients, 128 females (69.2%) and 57 males (30.8%), diagnosed with fibromyalgia participated in the study. The average age of the participants was 38.6, ranging from 18 to 65 years. The study was designed with relational screening and convenience sampling method. Fibromyalgia Impact Questionnaire (FIQ), Perth Alexithymia Questionnaire (PAQ), Childhood Trauma Questionnaire (CTQ), and socio-demographic data form were applied to the participants. The SPSS 25 program was used to examine the acquired data. Independent samples t-test, Pearson correlation analysis, and one way ANOVA were used.

Results: Results showed that childhood traumas and alexithymia predicted the effect level of fibromyalgia (49%), and alexithymia played a partial mediator role (8%) between childhood traumas and fibromyalgia impact level. It has been observed that emotional abuse ($p<.001$) and emotional neglect ($p=.002$) affect the effect level of fibromyalgia. It was discovered that the participants' degrees of fibromyalgia impact and alexithymia, and childhood traumas varied significantly by education and perceived income levels ($p<0.05$).

Conclusion: In addition to physiotherapy interventions in the treatment of fibromyalgia patients, focusing on the patients' traumatic childhood memories and helping them to recognize, express, and make sense of their emotions during the psychotherapy process will help alleviate the patients' pain intensity.

Keywords: Fibromyalgia, childhood traumas, emotional deafness, alexithymia

INTRODUCTION

Fibromyalgia is characterized by widespread muscle and bone pain and chronic fatigue accompanied by multiple symptoms (1). The prevalence of fibromyalgia is between 1% and 2% in the general population (2). It has comorbidity with various psychiatric disorders, significantly lowers the quality of life, and leads to an increase in diagnosis and treatment costs (3). Although no specific factor causing fibromyalgia has been reported, some associated factors exist, such as childhood traumas (1,4,5). There is cumulative trauma in patients with fibromyalgia (6). Patients exhibit symptoms of post-traumatic acute emotional stress (4). People with childhood traumas prefer to avoid an unanticipated unfavorable emotional shift or contrast experience when faced with unpleasant circumstances that stimulate their negative feelings (7). They struggle with recognizing, identifying, and expressing emotions (8).

Higher pain experience and alertness to pain are substantially connected with difficulty expressing feelings (9). Fibromyalgia patients exhibit higher levels of alexithymia than healthy individuals, and 48% have alexithymia (10). The avoidance of emotions in individuals with alexithymia is a major factor in both maintaining and aggravating fibromyalgia symptoms (11).

Cite this article: Çoban MC. Faraji H. The mediator role of alexithymia between childhood traumas and fibromyalgia impact level of patients with fibromyalgia . Interdiscip Med J. 2024;16(54):8-17. https://doi.org/10.17944/interdiscip.1541885

Corresponding Author: Dr. Haydeh Faraji, Haydeh Faraji, Istanbul Aydin University, Faculty of Science and Literature, Istanbul, Türkiye
E mail: haydehfaraji@aydin.edu.tr
ORCID iD: 0000-0001-5306-6546

Received: Sep 1, 2024
Accepted: Dec 20, 2024

Fonagy and Bateman state that the most negative effect on the child's distance from his/her own emotions is caregivers who cannot empathize with him/her (12). The key to the child's access to his/her emotions is primarily the parent's ability to access them. However, the presence of childhood traumas is evidence of the parent's dysfunction in this regard. In the presence of childhood traumas, the inability to process emotions can lead to the psychosomatization of existing negative emotions (13). However, childhood traumas are not enough by themselves to lead to psychosomatization (14). In this context, the current study is based on the idea that childhood traumas distract a child's emotional functioning, but when childhood wounds do not heal and children cannot develop proper emotional abilities though a child with childhood traumas tend to develop alexithymia. It has assumed that alexithymia, which indicates the adult's current emotional dysfunction in aspect of not being properly reaching emotions and being aware about them creates a tendency to express them with somatic symtoms like fibromyalgia. Therefore, the main hypothesis of the study is that there is a mediator role of alexithymia between childhood traumas and fibromyalgia. Also it is known that compared to individuals without alexithymia, those with chronic pain who were more likely to experience anxiety, pain catastrophizing, and low self-efficacy. It worsens the course of this disease (15). Therefore, understanding the role of alexithymia in fibromyalgia is essential for preventing that cascade effect of self-blaming. The results of this study may offer alternatives for the public benefit against the density of health institutions that result from frequent visits of people with fibromyalgia to polyclinics.

METHOD

Sample of the study

The sample size was calculated with the 'G. Power-3.1.9.4' programme at 95% confidence interval before data collection. In order for the mediating role to have an effective power level (0.8), a medium effect size (f2 = 0.15) and an alpha level of 0.05 for the two predictor variables, it was suggested that the number of participants required should be at least 55.

Linear multiple regression: Fixed model, single regression coefficient

Analysis: A priori: Compute required sample size

Input:	Tail(s)	=Two
	Effect size f^2	=0.15
	Alpha err prob	=0.05
	Power (1-beta err prob)	=0.80
	Number of predictors	=2
Output:	Noncentrality parameter delta	=2.8722813
	Critical t	=2.0066468
	Df	=52
	Total sample size	=55
	Actual power	=0.8048029

Adult fibromyalgia patients make up the study's population. Sample selection is made by convenience sampling. Convenience sampling was used to choose study participants from among fibromyalgia patients who applied to Physical Therapy and Compatibility Department of Cerrahpaşa Training and Research Hospital. An effort was made to reach the maximum patients as possible between 15th of December 2021 and the end of January 2022. During this time 227 patients gave their consent to participate in the study. However, 42 of them were disqualified from the study based on the exclusion criteria because they had co-occurring psychological health issues, and the remaining 185 participants' data were collected. The participants' ages ranged from 18 to 65. The data collection process was carried out in a closed envelope.

Data collection tools

The socio-demographic Data Form, the Childhood Trauma Questionnaire, the Fibromyalgia Impact Questionnaire, and the Perth Alexithymia Questionnaire were used to collect data from patients who voluntarily participated in the study.

Socio-demographic data form

Socio-demographic data form was constituted by the researcher and includes questions related to participants' age, gender, education level, perceived income level, and psychiatric diagnosis history.

Fibromyalgia impact questionnaire (FIQ)

The questionnaire was developed by Burckhardt et al. (16). It measures well-being, pain, fatigue, inability to work, difficulty at work, stiffness, morning fatigue, anxiety, and depression. Except for feeling well, low scores indicate less exposure to the disease. While each title could get a maximum of 10 points, the total score that could obtained in the test is 100. Its validity and reliability adaptation to Turkish was performed by Sarmer et al. (17). The Cronbach Alpha coefficient for this study was 0.88.

Perth alexithymia questionnaire (PAQ)

The Perth Alexithymia Questionnaire, which consists

of 24 items in a seven-point Likert type, was developed by Preece et al. (18) by integrating Gross's (19) extended emotion regulation theory. The scale works within the scope of the attention-evaluation model of alexithymia and includes five sub-dimensions. These are 'difficulty in recognizing negative emotions,' 'difficulty in recognizing positive emotions,' 'generally expressive thinking,' 'difficulty in expressing negative emotions,' and 'difficulty in expressing positive emotions'. Bilge (20) carried out the scale's adaptation to Turkish. High scores on the scale indicate high alexithymic characteristics. The scale's overall score had a 0.96 Cronbach's alpha internal consistency coefficient, and the subscales' alpha coefficients were between 0.85 and 0.90 (20). In this study the Cronbach Alpha coefficient of the total score of Alexithymia Scale was discovered to be 96.

Childhood trauma questionnaire (CTQ-33)

The questionnaire was developed by Bernstein et al. (21) to measure the childhood traumas of individuals. The 28-item, 5-point Likert scale arranged in reverse. The first Turkish adaptation of the questionnaire with 28 items, consisting of five dimensions as physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect, was made by Şar et al. (22). It was updated again with 33 items with the addition of the overprotection control sub-dimension after nine years (23). High scores obtained from the scale indicate that childhood traumas are high. In the original study, Cronbach's Alpha was calculated in the range of 0.79-0.94 for the scale and sub-dimensions. The adaptation study's relevant value was 0.80-0.89 (23). The overall Cronbach Alpha coefficient for the current study was 0.94; the subdimension scores were 90 for emotional abuse, 0.92 for physical abuse, 0.77 for physical neglect, 0.85 for emotional neglect, 0.90 for sexual abuse, and 0.89 for overprotection/control.

Process

Permission to use the scales and data on scale items and scoring procedures has been requested by the researchers who developed the scales or carried out the validity and reliability studies of the Turkish adaptation of the scales. Istanbul Aydin University Ethics Committee then reviewed the pertinent study to determine whether any ethical violations were found and gave its approval to the study and it started on December 1, 2021, with the number 2021/12 and the permission of the Cerrahpaşa Medical Faculty, Physical Therapy, and Rehabilitation Department, dated 15.12.2021 and numbered 263090. Helsinki Declaration rules were followed to conduct this study. Participants received an informed consent form and the study was conducted with those who read and accepted it. A questionnaire consisting of a sociodemographic data form, Perth Alexithymia Scale, Childhood Trauma Questionnaire, and Fibromyalgia Impact Questionnaire was applied to the participants who willingly took part in the study. The acquired data were moved into the computer environment.

Analysis of data

On the gathered data, a normality test analysis was done. The scale and sub-dimension total scores were observed to have normal and near-normal distributions. Tabachnick and Fidel (24) state that the assumption of a normal distribution is met by skewness and kurtosis values between +1.5 and -1.5. As a result of the findings obtained, parametric tests were used. Frequency analysis in examining the person and percentage distribution, descriptive statistics in examining the scale and sub-dimension total scores, to compare the mean scores of two independent categories, a sample t-test was utilized. One-way ANOVA test was utilized for examining the difference in mean scores between three variables. Using multiple linear regression and Pearson correlation analyses, the relationship between the sub-dimension scores was examined. Data analysis was done using the SPSS 25 (Statistical Package for Social Science).

RESULTS

Low and moderate positive correlations between the fibromyalgia impact and the alexithymia ($r=0.56$, $p<0.01$), childhood traumas ($r=0.67$, $p<0.01$), overprotection/control ($r=0.57$, $p<0.01$), sexual abuse ($r=0.28$, $p<0.01$), emotional abuse ($r=0.67$, $p<0.01$), emotional neglect ($r=0.64$, $p<0.01$), physical abuse ($r=0.39$, $p<0.01$), and physical neglect ($=0.48$, $p<0.01$) were detected (Table 1).

Low and moderate positive correlations were found between the variables alexithymia and childhood traumas ($r=0.53$, $p<0.01$), overprotection/control ($r=0.49$, $p<0.01$), sexual abuse ($r=0.18$, $p<0.05$), emotional neglect ($r=0.47$, $p<0.01$), emotional abuse ($r=0.49$, $p<0.01$), physical abuse ($r=0.30$, $p<0.01$), physical neglect ($r=0.47$, $p<0.01$) (Table 1).

Upon reviewing the regression table's findings, it is seen that the independent variables of emotional abuse, physical abuse, emotional neglect, and sexual abuse do not have a significant predictive effect on alexithymia. In addition, physical neglect and overprotection/control variables predict alexithymia. Thirty percent of the variance in the outcome variable ($F(6.178)=14.26$, $p<0.001$) can be explained by the predictors, according to the R2 value of.30. The results demonstrated that overprotection/control (Beta=0.22 $p<0.05$) and physical neglect (Beta=0.27 $p<0.01$) are positive predictors of alexithymia (Table 2).

Upon examining the regression table's results, it is seen that

the independent variables of physical harassment, physical neglect, sexual harassment, and overprotection/control do not have a significant prediction on the fibromyalgia effect. On the other hand, emotional abuse and emotional neglect variables predict the fibromyalgia effect. With an R2 value of .48, it can be observed that 48% of the variance in the outcome variable is explained by the predictors ($F(6.178)=29.35$, $p<0.001$). The results indicate that the fibromyalgia impact is positively predicted by emotional abuse (Beta=0.44 $p<0.001$) and by emotional neglect (Beta=0.30 $p<0.01$) (Table 3).

In the first model, the childhood traumas scale explained 41% of the variance in the Fibromyalgia Impact Questionnaire's score, the Alexithymia Questionnaire was introduced to the model in the second stage. It was demonstrated that alexithymia was accounted for 8% of the variance score of the fibromyalgia effect. The results showed that childhood traumas and alexithymia explained 49% of the variance in the impact of fibromyalgia. With the addition of the alexithymia, the beta value of the childhood trauma decreased from 0.65 to 0.49. Five thousand resampling choices and 95% confidence interval options from Bootstrapping analysis were then used to control this decrease in beta value. It was discovered that the result did not include "0" (zero) for either the bottom or upper bounds. According to the results of the mediator role study, it was established that there was only partial mediation (Table 4 & Figure 1).

Table 1. Investigation of the relationship between age, fibromyalgia, perth alexithymia, childhood traumas

	1	2	3	4	5	6	7	8	9	10
1- Age	1									
2- Fibromyalgia	0.04	1								
3- Alexithymia	0.15*	0.56**	1							
4- Childhood Traumas	-0.06	0.67**	0.53**	1						
5- Emotional Abuse	-0.04	0.67**	0.49**	0.91**	1					
6- Physical Abuse	0.04	0.39**	0.30**	0.67**	0.61**	1				
7- Physical Neglect	-0.04	0.48**	0.47**	0.78**	0.61**	0.48**	1			
8- Emotional Neglect	-0.02	0.64**	0.47**	0.90**	0.77**	0.52**	0.71**	1		
9- Sexual Abuse	-0.23**	0.28**	0.18*	0.60**	0.46**	0.31**	0.44**	0.48**	1	
10- Over Protection/Control	-0.05	0.57**	0.49**	0.82**	0.74**	0.40**	0.51**	0.70**	0.33**	1

Table 2. Prediction of childhood traumas in the alexithymia

						%95 CI	
	B	SE	Beta	t	p	LL	UL
Constant	1.95	0.19		10.02	<0.001***	1.57	2.33
Emotional Abuse	0.03	0.02	0.20	1.67	0.097	-0.01	0.07
Physical Abuse	-0.01	0.02	-0.03	-0.33	0.742	-0.05	0.04
Physical Neglect	0.07	0.02	0.27	2.98	0.003**	0.02	0.11
Emotional Neglect	0.01	0.02	0.04	0.39	0.697	-0.03	0.05
Sexual Abuse	-0.03	0.02	-0.11	-1.57	0.118	-0.07	0.01
Over Protection/Control	0.04	0.02	0.22	2.27	0.024*	0.00	0.07
$R=0.57$ $R^2=0.30$ $F_{(6.178)}=14.26$ $p<.001$***							

***p<.001, **p<.01, *p<.05; Note, CI: Confidence Interval, B: Regression coefficient, SE: Standard Error, t: t-statistic, p: p-value, LL: Lower Limit, UL: Upper Limit, R: Correlation coefficient, R^2: Coefficient of Determination, F: F-statistic

Table 3. Prediction of childhood traumas in the fibromyalgia impact

						95%	
	B	SE	Beta	t	p	LL	UL
Constant	2.35	0.18		13.21	<0.001***	2.00	2.70
Emotional Abuse	0.08	0.02	0.44	4.29	<0.001***	0.04	0.11
Physical Abuse	-0.02	0.02	-0.05	-0.76	0.451	-0.06	0.03
Physical Neglect	0.01	0.02	0.03	0.40	0.691	-0.03	0.05
Emotional Neglect	0.06	0.02	0.30	3.07	0.002**	0.02	0.09
Sexual Abuse	-0.03	0.02	-0.09	-1.44	0.151	-0.07	0.01
Over Protection/Control	0.01	0.02	0.07	0.79	0.430	-0.02	0.04
$R=0.71$ $R^2=0.48$ $F_{(6.178)}=29.35$ $p<.001$***							

***p<.001, **p<.01, *p<.05; Note, CI: Confidence Interval, B: Regression coefficient, SE: Standard Error, t: t-statistic, p: p-value, LL: Lower Limit, UL: Upper Limit, R: Correlation coefficient, R^2: Coefficient of Determination, F: F-statistic

Table 5 displays the results of the one-way ANOVA test analysis to see if there is a difference between the participants' educational levels and the average total scores on the childhood traumas, perth alexithymia, and fibromyalgia impact. It was discovered that the participants' degrees of fibromyalgia impact, degrees of alexithymia, and childhood traumas varied significantly by levels of education ($p<0.05$) (Table 5).

The Tukey test evaluated which groups of education levels had a significant difference. According to the test results, fibromyalgia impact level differs between primary school graduates (4.4756±85765) and high school graduates (3.9468±.76178), undergraduate graduates (3.6246±.76299) and graduate (3.6667 ±.73866) groups ($p<0.05$). The fibromyalgia impact level differs between high school graduates (3.9468±.76178) and primary school graduates (4.4756±85765) groups ($p<0.05$). Fibromyalgia impact level differs between undergraduates (3.9468±.76178) and primary school graduates (4.4756±85765) groups ($p<0.05$). It differs between postgraduates (3.6667±.73866) and primary school graduates (4.4756±85765) groups ($p<0.05$) (Table 5).

Table 6 shows the results of the one-way ANOVA test analysis to determine whether there is a difference between the Fibromyalgia Impact Questionnaire, Perth Alexithymia Scale, childhood traumas, and sub-dimension total score averages according to the economic level of the participants. It was observed a statistically significant difference between the economic levels of the participants and the level of fibromyalgia impact, alexithymia level, and childhood traumas ($p<0.05$) (Table 6).

The Tukey test assessed which groups of economic levels had a significant difference. The fibromyalgia impact level showed a significant difference between the low-income level (4.3547±.8442), middle-income level (3.8170±.83846), and high-income level (3.7488±.72836) groups ($p<0.05$). Between the middle-income (3.8170±.83846) and low-income (4.3547±.8442) groups, there was a statistically different level of fibromyalgia impact ($p<0.05$). Between the high-income (3.7488±.72836) and low-income (4.3547±.8442) groups, there was a statistically different level of fibromyalgia impact ($p<0.05$) (Table 6).

The low-income (2.4049±.5948), middle-income (2.1264±.4792), and high-income (1.9090±.3739) groups differed statistically significantly ($p <0.05$) in terms of childhood traumas. Between the groups with moderate incomes (2.1264±.4792) and low incomes (2.4049±.5948), there existed a statistically significant variation in the degree of childhood traumas. Also, childhood traumas were significantly different between the high-income (1.9090±.3739) and low-income (2.4049±.5948) groups ($p<0.05$) (Table 6).

Table 4. Results on the role of the alexithymia as a tool for the childhood traumas' predictions of the fibromyalgia

Model		R	R^2	B	SH	Beta	t	p	Lower Bound	Upper Bound
1	(Constant)	0.29	0.41	2.28	0.16		13.95	0.000	1.96	2.60
	Childhood Traumas			0.04	0.00	0.65	11.48	0.000	0.03	0.04
2	(Constant)	0.36	0.49	1.58	0.21		7.71	0.000	1.18	1.99
	Childhood Traumas			0.03	0.00	0.49	8.06	0.000	0.02	0.04
	Alexithymia			0.33	0.06	0.31	5.10	0.000	0.20	0.46
	Undirect Total Effect (Mediator)			0.01	0.00				0.01	0.02

*p<0.05 Test used: PROCESS 3.5, R: Correlation coefficient, R^2: Coefficient of determination, B: Regression coefficient (Beta coefficient), Standardized regression coefficient, t: t-statistic, p: Significance value (p-value), Lower Bound: The lower limit of the 95% confidence interval, Upper Bound: The upper limit of the 95% confidence interval, Undirect Total Effect (Mediator): The total indirect effect

Table 5. One-Way ANOVA test by education level

Scale/Sub-Dimension	df	Mean Square	F	P
Fibromyalgia	3	7.296	11.414	0.001**
Alexithymia	3	6.870	12.213	0.001**
Childhood Traumas	3	3.033	11.477	0.001**

** p<.001 * p<.05, df :Degrees of Freedom, F: F-Statistic (F-value), P :P-Value

Table 6. One-Way ANOVA test by income level

Scale/Sub-Dimension	df	Mean Square	F	P
Fibromyalgia	2	7.400	10.969	0.001**
Alexithymia	2	6.418	10.658	0.001**
Childhood Traumas	2	3.550	12.964	0.001**

** p<.001 * p<.05, df :Degrees of Freedom, F: F-Statistic (F-value), P :P-Value

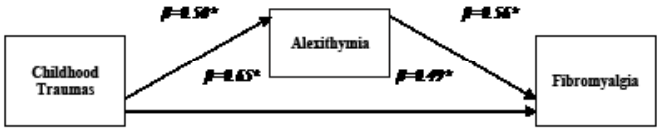

Figure 1. Beta coefficients for the role of the alexithymia as a tool for the childhood traumas predictions of the Fibromyalgia

There was a statistically significant difference in the level of alexithymia between the low-income (3.6268±.6911) and high-income (2.9236±.8855) groups ($p<0.05$). Between the middle-income (3.3829±.8287) and high-income (2.9236±.8855) groups, there was a statistically significant difference in the level of alexithymia ($p<0.05$). Between the high-income (2.9236±.8855), low-income (3.6268±.6911), and middle-income (3.3829±.8287) groups, there was a statistically significant difference in alexithymia level ($p<0.05$) (Table 6).

Results of the comparison of fibromyalgia impact questionnaire, perth alexithymia scale, childhood trauma scale scores with independent samples T-test

When the scores from the Fibromyalgia Impact Questionnaire, Perth Alexithymia Questionnaire, Childhood Trauma Questionnaire, emotional abuse, physical abuse, physical neglect, emotional neglect, sexual abuse, and overprotection/control sub-dimensions were analyzed according to gender and there was no significant difference between the compared groups ($p>0.05$).

DISCUSSION

This study's primary hypothesis-which is supported by the data-was that alexithymia functions as a mediator between fibromyalgia and childhood trauma. Emotional neglect and abuse and alexithymia levels predict fibromyalgia level, and alexithymia played a mediator role between childhood traumas and fibromyalgia. The finding that emotional neglect and abuse, which are types of childhood abuse, predict fibromyalgia demonstrates the central role of impairment in emotional functioning in fibromyalgia. Emir et al. (25) emphasize that people who suffer from fibromyalgia have experienced childhood trauma and struggle to communicate their feelings. Similar to this study, it is stated that psychological abuse and neglect are associated with difficulty in defining emotions, are seen at higher levels in fibromyalgia patients, and predict alexithymia (26). Adamowicz et al. (27) state that alexithymia plays an important role between childhood traumas and psychosomatic disorders. Brown et al. (28) found that emotional abuse is associated with difficulty describing feelings, and emotional neglect is with difficulty identifying feelings. According to one theory, parents of neglected and emotionally abused children are unable to recognize, express, or differentiate between different emotions and they become unable to develop emotion-related skills for themselves and other people (28,29).

Children who maltreated show deficits in emotion recognition, expression, and understanding (30). Kick et al. (31) discovered a connection between alexithymia and child maltreatment, as well as a tie between alexithymia and general psychopathology. The results of the study conducted with 430 detainees in China similarly reveal the relationship between childhood traumas and alexithymia (32). This study shows that over protection/control and psyhsical abuse types of chilhood trauma predict alexithymia. However, literature mainly states emotional abuse and neglect experiences for the development of alexithymia (26, 30). Since emotional neglect and abuse are found at certain rates in all types of childhood trauma, it is thought that the inconsistency between the current study and other studies in the literature does not reflect an inconsistency in content. Also it is known that individuals with high levels of alexithymia tend to address external physical experiences rather than internal emotional experiences due to their emotional blindness that might be another explanation of the inconsistency between the current study and the literature.

Significant conditional indirect effects of emotional abuse and neglect in childhood have discovered to have an impact on psychopathology, and the size of this link increases with greater levels of alexithymia (33). Also, alexithymia predicts the likelihood of having fibromyalgia (34). In a study on the expression of emotions, it was reported that 40% of fibromyalgia patients had difficulty expressing their emotions, and 24% had difficulty defining emotions (11). Alexithymia is stated as the determinant of pain intensity and physical interference of patients diagnosed with fibromyalgia (10,26,35). It has found that alexithymic fibromyalgia patients have higher pain levels than non-alexithymic patients (36,37).

In this study, the decrease in perceived income and educational level was found to be associated with the increase in the level of childhood traumas, alexithymia, and fibromyalgia. It has been found that perceived low-income levels are linked to high levels of alexithymia and that low levels of education are linked to higher levels of alexithymia in addition to perceived low-income levels (38). According to Han et al. (39), alexithymia and socioeconomic class were related. Alexithymia is more common in people with lower levels of education and monthly household income. Higher educational level is associated with higher health literacy, indicating that the increase in health literacy levels decreased the level of alexithymia (40,41). It has been found that people with lower levels of education had more severe

fibromyalgia symptoms (42-44). An increase in education can make it easier for an individual to have an environment that is more respectful of their existence and can increase their independence and capacity to understand themselves. It is thought that having a lower level of education is associated with higher levels of alexithymia, as it can lead to the opposite results, alienating the individual from an environment where their ability to recognize and express their emotions can develop.

It is seen that the perceived low-income level of the family or country is also a risk factor for childhood trauma, and the presence of childhood trauma is a risk factor for fibromyalgia (5,45,46). In this study, it was observed that the effect of fibromyalgia increased as the income level decreased. The study of Mathkor and Atwan (47) found that widespread pain was higher in the low socioeconomic group than in the high socioeconomic group. In comparison, the diagnosis of fibromyalgia was similarly higher in the low socioeconomic group than in the high socioeconomic group (47). Another study stated that low socioeconomic status was associated with symptom severity and functional impairment in fibromyalgia (43). The incidence of fibromyalgia in the poor socioeconomic group is attributed to factors including restricted access to health services, difficulties following medical advice, indirect health expenditures, and a lack of financial mean for healthy lifestyle choices like sufficient eating (48).

Although it is known that the psychosocial effects of fibromyalgia are the same in men and women, Cooksey and Choy (49) report that it generally effects women (80-90% of all cases). Theyexplain this by the fact that men are less likely to seek treatment. Similarly, in this study, female patients with fibromyalgia were the majority, but no difference was found between the level of fibromyalgia impact according to the gender of the participants. This result may explain the higher rates of fibromyalgia among women, especially in the Turkish pupolation, as women are more likely to take part in unpaid domestic work as a result of the fact that women are responsible for housework and childcare.

Limitations of the study

In the current study, 64 (32.6%) participants had a psychiatric diagnosis, and 121 (65.4%) did not have a psychiatric diagnosis before. However, the fact that the participants were not evaluated for the diagnoses they received and that the effect of the accompanying diagnosis on fibromyalgia could not be determined is the limitation of the study.

CONCLUSION

This study found that emotional neglect and abuse and alexithymia level predict fibromyalgia level, and alexithymia played a mediator role between childhood traumas and fibromyalgia. In light of these findings, it is assumed that providing fibromyalgia patients with psychological support, focusing on their traumatic childhood experiences, and identifying, expressing, and making sense of emotions during the psychotherapy process will help them suffer less. The study's secondary results indicate that rise in perceived income level and educational level accompany by fall in fibromyalgia and alexithymia. Being educated and being able to earn enough money for oneself work as a support system, which individuals get from themselves. Also, when individuals are not dependent on somebody else for living, they tend to be more free to express themselves without concern. Therefore, these results reveal that supporting children for their education and serving job oppurtunities may work as a preventive and palliative system.

This study follows fibromyalgia patients who apply to the physical therapy outpatient clinic. It offers an alternative to reducing the workforce of physical therapy doctors who have difficulty planning their treatment. Working with psychologists and healthcare professionals simultaneously will benefit the fibromyalgia patient group. Longitudinal studies on this subject, which will be carried out in the future, will help to understand this issue.

ACKNOWLEDGEMENT

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Thesis: This study was produced from the clinical psychology master's thesis conducted by MCÇ under the supervision of HF

Ethical Declaration: Ethical permission was obtained from the İstanbul Aydın University ethics committee for this study with date December 1, 2021 and number 2021 and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions: Concept: MCÇ, HF, Design: MCÇ, HF, Supervising: HF, Financing and equipment: MCÇ, Data Collection and entry- MCÇ, Analysis and Interpretation: MCÇ, HF, Literatur search: HF, MCÇ, Writing: HF, MCÇ, Critical Review: HF

REFERENCES

1. Boussi-Gross R, Catalogna M, Lang E, Shamai Z, Ablin JN, Aloush V, et al. Hyperbaric oxygen therapy vs.

pharmacological intervention in adults with fibromyalgia related to childhood sexual abuse: prospective, randomized clinical trial. Sci Rep. 2024;14(1):11599. https://doi.org/10.1038/s41598-024-62161-5

2. Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. Rheumatol Int. 2017;37:1527-39. https://doi.org/10.1007/s00296-017-3725-2

3. Husak AJ, Bair MJ. Chronic pain and sleep disturbances: a pragmatic review of their relationships, comorbidities, and treatments. Pain Medicine. 2020;21(6):1142-52. https://doi.org/10.1093/pm/pnz343

4. Sandoval NB, Solà JF, Mateo AG, Durán MPN, Urrea LAM, Belmonte ST, et al. Design and validation of a predictive model for determining the risk of developing fibromyalgia. Clin Exp Rheumatol. 2023;1:1238-47.

5. Combas M, Ozturk E, Derin G. Childhood trauma and dissociation in female patients with fibromyalgia. Medicine. 2022;11(4):1635-40. https://doi.org/10.5455/medscience.2022.09.211

6. Romeo A, Tesio V, Ghiggia A, Di Tella M, Geminiani GC, Farina B, et al. Traumatic experiences and somatoform dissociation in women with fibromyalgia. Psychol Trauma. 2022;14(1):116-23. https://doi.org/10.1037/tra0000907.

7. Shafiei M, Rezaei F, Sadeghi M. The role of childhood traumas, interpersonal problems, and contrast avoidance model in development of the generalized anxiety disorder: A structural equation modeling. Psychol Trauma. 2022;14(3):377–85. https://doi.org/10.1037/tra0001117

8. Gul H, Torun YT, Cakmak FH, Gul A. Facial emotion recognition in adolescent depression: The role of childhood traumas, emotion regulation difficulties, alexithymia and empathy. Indian J Psychiatry. 2023;5(4):443-52. https://doi.org/10.4103/indianjpsychiatry.indianjpsychiatry_284_22

9. Martínez MP, Sánchez AI, Miró E, Lami MJ, Prados G, Morales A. Relationships between physical symptoms, emotional distress, and pain appraisal in fibromyalgia: The moderator effect of alexithymia. J Psychol.2015;149(2):115-40. https://doi.org/10.1080/00223980.2013.844673

10. Asgarabad HM, Yegaei PS, Jafari F, Azami-Aghdash S, Lumley MA. The Relationship of Alexithymia to Pain and Other Symptoms in Fibromyalgia: A Systematic Review and Meta-analysis. Eur J Pain. 2022;27(3):1-17 https://doi.org/10.1002/ejp.2064

11. Trucharte A, Leon L, Castillo-Parra G, Magán I, Freites D, Redondo M. Emotional regulation processes: influence on pain and disability in fibromyalgia patients. Clin Exp Rheumatol. 2020;38(123):40-46.

12. Fonagy P, Bateman AW. Adversity, attachment, and mentalizing. Compr Psychiatry. 2016;64:59-66. https://doi.org/10.1016/j.comppsych.2015.11.006

13. Eilers H, aan het Rot M, Jeronimus BF. Childhood trauma and adult somatic symptoms. Psychosom Med. 2023; 85(5): 408-16. https://doi.org/10.1097/PSY.0000000000001208

14. Güleç MY, Altintaş M, İnanç L, Bezgin ÇH, Koca, EK, Güleç H. Effects of childhood trauma on somatization in major depressive disorder: The role of alexithymia. J Affect Disord. 2013;146(1):137-41. https://doi.org/10.1016/j.jad.2012.06.033

15. Pei JH, Wang X, Ma T, Du Y, Dou X. Alexithymia in a Chinese patient with chronic pain and associated factors: A cross-sectional study. Pain Manag Nurs. 2023;24(4):1-6. https://doi.org/10.1016/j.pmn.2023.01.003

16. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: Development and validation. J Rheumatol Suppl. 1991;5:728-33.

17. Sarmer S, Ergin S. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int. 2000;20:9-12. https://doi.org/10.1007/s002960000077

18. Preece D, Becerra R, Robinson K, Dandy J, Allan A. The psychometric assessment of alexithymia: Development and validation of the Perth Alexithymia Questionnaire. Res Autism Spectr Disord. 2018;132:32-44. https://doi.org/10.1016/j.paid.2018.05.011

19. Gross JJ. Emotion regulation: Current status and future prospects. Psychol Inq. 2015;26(1):1-26. https://doi.org/10.1080/1047840X.2014.940781

20. Bilge Y. The measurement of attention-appraisal modal of alexithymia: psychometric properties of the Perth Alexithymia Questionnaire in Turkish. Anadolu Psikiyatri Derg. 2020;21(2):71-9. https://doi.org/10.5455/apd.133183

21. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J

Psychiatry. 1994;151(8):1132-6. https://doi.org/10.1176/ajp.151.8.1132

22. Şar V, Öztürk E, İkikardeş E. Validity and reliability of the Turkish Version of the Childhood Trauma Questionnaire (CTQ). Turkiye Klinikleri Journal of Medical Sciences. 2012;32(4):1054-63.

23. Şar V, Necef I, Mutluer T, Fatih P, Türk-Kurtça T. A revised and expanded version of the Turkish Childhood Trauma Questionnaire (CTQ-33): Overprotection-overcontrol as additional factor. J Trauma Dissociation. 2021 22(1):35-51. https://doi.org/10.1080/15299732.2020.1760171

24. Tabachnick BG, Fidell LS. Using Multivariate Statistics. Pearson. 2013.

25. Emir BS, Yıldız S, Sehlikoğlu Ş, Çakmak E, Gözel N. An Investigation of Alexithymia, Type D Personality Traits, and Childhood Traumas in Patients with Fibromyalgia. SAS J. Med. 2023;8:873-9. https://doi.org/10.36347/sasjm.2023.v09i08.013

26. Ditzer J, Wong EY, Modi RN, Behnke M, Gross JJ, Talmon A. Child maltreatment and alexithymia: A meta-analytic review. Psychol Bull. 2023;149(5-6):311. https://doi.org/10.1037/bul0000391

27. Adamowicz JL, Sirotiak Z, Thomas EBK. Childhood maltreatment and somatic symptoms: Examining the role of specific types of childhood maltreatment and alexithymia. Psychol Trauma. 2022; Advance online publication. https://doi.org/10.1037/tra0001315

28. Brown S, Fite PJ, Stone K, Richey A, Bortolato M. Associations between emotional abuse and neglect and dimensions of alexithymia: The moderating role of sex. Psychol Trauma. 2018;10(3):300-8.

29. Schimmenti A. The developmental roots of dissociation: A multiple mediation analysis. Psychoanalytic Psychology. 2017;34:96-105.

30. Khan AN, Jaffee SR. Alexithymia in individuals maltreated as children and adolescents: a meta-analysis. J Child Psychol Psychiatry. 2022;63(9):963-72. https://doi.org/10.1111/jcpp.13616

31. Kick L, Schleicher D, Ecker A, Kandsperger S, Brunner R, Jarvers I. Alexithymia as a mediator between adverse childhood events and the development of psychopathology: a meta-analysis. Front Psychiatry. 2024;15:1412229. https://doi.org/10.3389/fpsyt.2024.1412229

32. Chen P, Sun X, Zhang Q, Yang C, Ye X, Wang Y, et al. Alexithymia and depressive symptoms mediated the relationship between childhood trauma and suicidal risk in Chinese male prisoners. Curr Psychol. 2022;42: 29023-34. https://doi.org/10.1007/s12144-022-03975-2

33. Krvavac S, Jansson B. The role of emotion dysregulation and alexithymia in the link between types of child abuse and neglect and psychopathology: A moderated mediation model. European Journal of Trauma & Dissociation. 2021;(3):100213. https://doi.org/10.1016/j.ejtd.2021.100213

34. Romeo A, Di Tella M, Ghiggia A, Tesio V, Fusaro E, Geminiani GC, Castelli L. Attachment style and parental bonding: Relationships with fibromyalgia and alexithymia. PloS One. 2020;15(4):e0231674. https://doi.org/10.1371/journal.pone.0231674

35. Aaron RV, Fisher EA, De La Vega R, Lumley MA, Palermo TM. Alexithymia in individuals with chronic pain and its relation to pain intensity, physical interference, depression, and anxiety: A systematic review and meta-analysis. Pain. 2019;160(5):994-1006. https://doi.org/10.1097/j.pain.0000000000001487

36. Marchi L, Marzetti F, Scotto J, Cesari V, Baroni M, Miccoli M, et al. Alexithymia, negative affective states and pain in patients with fibromyalgia: An experımental study. MJCP. 2019;7(2):93-4.

37. Di Tella M, Castelli L. Alexithymia in chronic pain disorders. Curr Rheumatol Rep. 2016;18:1-9. https://doi.org/10.1007/s11926-016-0592-x

38. Obeid S, Akel M, Haddad C, Fares K, Sacre H, Salameh P, Hallit S. Factors associated with alexithymia among the Lebanese population: Results of a cross-sectional study. BMC Psychol. 2019;7(80):1-10. https://doi.org/10.1186/s40359-019-0353-5

39. Han D, Lu Y, Huang R, Yang Z, Peng G, Qiao Y, et al. Acupuncture for fibromyalgia: A review based on multidimensional evidence. Am J Chin Med. 2023;51(2):1-29. https://doi.org/10.1142/S0192415X23500143

40. Bozbulut R, Soysal Acar AŞ, Döğer E, Orhun Çamurdan M, Bideci A. The relationship between alexithymia, health literacy, and diet quality in obese adolescents. J Pediatr Endocrinol Metab. 2023;36(2):137-46. https://doi.org/10.1515/jpem-2022-0405

41. Estrela M, Semedo G, Roque F, Ferreira PL, Herdeiro MT. Sociodemographic determinants of digital health literacy: A systematic review and meta-analysis. International Journal of Medical Informatics. 2023;177:105124. https://doi.org/10.1016/j.ijmedinf.2023.105124

42. Atzeni F, Alciati A, Bazzichi L, Govoni M, Biasi G, Di Franco M, et al. Sociodemographic factors in fibromyalgia: Results from the Italian Fibromyalgia Registry. Clin Exp Rheumatol. 2022;40(6):1183-8. https://dx.doi.org/10.55563/clinexprheumatol/64963d

43. Fitzcharles MA, Rampakakis E, Ste-Marie PA, Sampalis JS, Shir Y. The association of socioeconomic status and symptom severity in persons with fibromyalgia. J Rheumatol Suppl.. 2014;41(7):1398-1404. https://doi.org/10.3899/jrheum.131515

44. Benebo FO, Lukic M, Jakobsen MD, Braaten TB. The role of lifestyle factors in the association between education and self-reported fibromyalgia: a mediation analysis. BMC Womens Health. 2024;24(244):1-12. https://doi.org/10.1186/s12905-024-03060-9

45. Cantürk M, Faraji H. Tezcan AE. The relatıonshıp between chıldhood trauma and crıme ın male prısoners, Alpha Psychiatry. 2021;22(1):56-60. https://doi.org/10.5455/apd.111825

46. Bauer A, Fairchild G, Hammerton G, Murray J, Santos IS, Rodrigues LT, et al. Associations between childhood trauma and childhood psychiatric disorders in Brazil: A population-based, prospective birth cohort study. Lancet Psychiatry. 2022;9(12):969-77. https://doi.org/10.1016/S2215-0366(22)00337-6

47. Mathkhor AJ, Atwan AH. Fibromyalgia syndrome and its allied clinical features are associated with low socioeconomic status. Int J Clin Rheumtol. 2022;17(11):155-60.

48. Metwally RS, Abdullah AA, AlAmmar WA, Sebastian T. Are dietary pattern associated with alexithymia in Saudi adults? Nutr Health. 2024;30(2):291-300. https://doi.org/10.1177/02601060221115508

49. Cooksey R, Choy E. Exploring gender differences, medical history, and treatments used in patients with fibromyalgia in the UK using primary-care data: A retrospective, population-based, cohort study. Lancet Rheumatol. 2022;4: 20. https://doi.org/10.1016/S2665-9913(22)00296-X

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1467199
Interdiscip Med J 2025;16(54):18-24

Adiponectin and Lone atrial fibrillation

Özden Kutlay[1], Arzu Keskin Aktan[1], Zafer Yalım[2]

[1]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Physiology, Afyonkarahisar, Türkiye.
[2]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Cardiology, Afyonkarahisar, Türkiye.

Abstract

Objective: Lone atrial fibrillation is an idiopathic arrhythmia seen in younger individuals without any secondary disease. Adiponectin is an endogenous adipocytokine that increases insulin sensitivity with anti-inflammatory and anti-proliferative effects. Although the relationship between circulating adiponectin and atrial fibrillation has been suggested, it is questionable whether this relationship is arrhythmia-related. Therefore, the focus of this study is to investigate the relationship between adiponectin and Lone atrial fibrillation.
Methods: In this prospective study, 26 healthy individuals in sinus rhythm, 34 patients with Lone Atrial Fibrillation, and 38 patients diagnosed with Atrial Fibrillation were included by questioning their cardiovascular histories and risk factors upon their arrival at the hospital. Echocardiography was performed to evaluate the left ventricular ejection fraction. Plasma adiponectin levels were studied with Enzyme-Linked ImmunoSorbent Assay (ELISA).
Results: Plasma adiponectin levels were significantly lower in the Atrial Fibrillation and Lone Atrial Fibrillation groups compared to the control group ($p<0.001$, $p<0.001$). Adiponectin levels did not differ significantly between Atrial Fibrillation and Lone Atrial Fibrillation groups ($p=0.191$). Furthermore, adiponectin was positively correlated with left ventricular ejection fraction ($r=0.208$, $p=0.04$).
Conclusion: This study reveals, for the first time, the relationship between plasma adiponectin levels and Lone Atrial Fibrillation. Our results indicated that low adiponectin levels are associated with Lone Atrial Fibrillation and that this relationship persists in patients with secondary Atrial Fibrillation. Therefore, we predict that adiponectin decreases in Atrial Fibrillation due to arrhythmia independent of secondary diseases.
Keywords: Atrial fibrillation, Lone atrial fibrillation, adiponectin, arrhythmia, left ventricular ejection fraction

INTRODUCTION

Atrial fibrillation (AF) emerges as one of the most prevalent arrhythmias, affecting 3-4% of the population and leading to increased morbidity and mortality, along with a heightened risk of stroke (1, 2). Well-defined major risk factors for AF include advanced age, hypertension, congestive heart disease (CHD), diabetes mellitus (DM), and thyroid disease (TD) (3). AF frequently arises as a secondary manifestation, either linked to a cardiac-origin condition like acute coronary syndrome and heart failure or associated with extracardiac comorbidities such as infectious or chronic lung disease (4). However, AF, usually observed in a proportion of young individuals, develops as an unexplained or idiopathic primary disorder called “lone AF” without an identifiable trigger (2). By general convention, the subtype of AF identified in individuals under the age of 60, where clinical assessment and imaging methods exclude structural cardiopulmonary diseases like coronary artery disease (CAD), hypertension, and heart valve disease, is termed lone AF. The typical age of individuals undergoing treatment for Lone AF within the young and middle-aged demographic hovers around 44 (5). Adiponectin is an endogenous adipocytokine with positive effects on cardiovascular diseases, and it stands out as a potential risk marker for AF (6,7). Adiponectin levels in plasma are reduced in obese individuals, patients with type 2 DM, CAD, and hypertension (8). Nevertheless, certain studies have linked elevated circulating adiponectin levels

Cite this article: Kutlay Ö, Keskin-Aktan A, Yalım Z. Adiponectin and Lone atrial fibrillation. Interdiscip Med J. 2025;16(54):18-24. https://doi.org/10.17944/1467199

Corresponding Author: Dr. Özden Kutlay, Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Physiology, Afyonkarahisar, Türkiye
Email: ozden.kutlay @afsu.edu.tr
ORCID iD: 0000-0001-5509-6650

Received: Apr 9, 2024
Accepted: Feb 1, 2025

with an unfavorable prognosis in conditions like heart failure, coronary heart disease, and cardiovascular disease (6,7). Furthermore, certain researchers have underscored a notable association between adiponectin and AF, suggesting that elevated adiponectin levels might pose a risk factor for AF (6, 8-10). The findings from these studies prompt us to hypothesize that the levels of adiponectin play a role in shaping the development and prevalence of AF.

According to the information provided by studies so far, the uncertainty persists regarding whether the elevated adiponectin levels observed in patients with secondary AF accompanied by secondary diseases are a consequence of AF itself or a result of hypertension, diabetes, or cardiac diseases associated with AF. Consequently, the goal of this study is to investigate the plasma adiponectin levels in patients with Lone AF who do not have any accompanying diseases. The increasing interest in the role of biomarkers in the pathogenesis and prognosis of AF is notable. However, there is still limited data on biomarkers in Lone AF (11). Accurately identifying patients with true Lone AF, meaning those at genuinely low risk of complications, holds significant prognostic and therapeutic implications. This study will be the first to demonstrate a possible relationship between adiponectin and Lone AF.

METHOD

Patients who previously applied to the Afyonkarahisar Medical Faculty Cardiology Department with complaints of palpitations and were diagnosed with Lone AF and AF underwent routine follow-ups. Thirty-four participants with Lone AF, 38 with AF, and 26 entirely healthy individuals in sinus rhythm were enrolled in the control group, sorted based on their arrival sequence. The patients' cardiovascular histories and risk factors were thoroughly examined, and detailed physical examinations were performed. Baseline electrocardiograms (ECGs) were taken for all patients and controls involved in the evaluation. Transthoracic echocardiography was performed in all study participants to assess the left ventricular ejection fraction and exclude heart valve disease.

Exclusion criteria for the Lone AF group included systolic heart failure ejection fraction (EF)<45%), diastolic heart failure, dilated and hypertrophic cardiomyopathy, congenital heart disease, restrictive cardiomyopathy, AF associated with valvular diseases, patients with mechanical valves, post-op AF, chronic liver disease, chronic kidney insufficiency, malignancy, arthritis, infection, CAD, hypertension, diabetes, thyroid disease, and individuals with inflammatory and autoimmune diseases.

Twenty-six completely healthy volunteers, meticulously selected for gender balance, constituted the control group. Exclusion criteria for the control group involved the detection of organic heart disease, suspected inflammation, infection, or chronic lung disease through routine echocardiography and physical examination. The execution of this study adhered to the principles of the Declaration of Helsinki, following the approval of the institutional ethics committee (Ethics committee date/number: Date:05.08.2022/ Number:2022/428).

Echocardiography

Two-dimensional echocardiography and Doppler echocardiography were conducted by an experienced echocardiographer using the Vivid 3 device (GE Healthcare Systems, Piscataway, New Jersey, USA) in all patients and the control group. Measurements included left ventricular systolic and diastolic diameters, left atrial dimensions, volumes, and the left ventricular ejection fraction.

Plasma adiponectin measurement

A peripheral blood sample was obtained from both the patient and control groups during the morning hours of 9:00-10:00, following an overnight fast of 8-12 hours. The samples underwent centrifugation at 4000xg for 10 minutes, leading to the separation of plasma. The plasma samples were subsequently preserved at -80 °C until the moment of biochemical analysis, aiming to ascertain the adiponectin levels. Furthermore, blood samples were gathered from each patient for routine biochemistry analysis. The amount of plasma adiponectin was measured using the human adiponectin ELISA kit from Bioassay Technology Laboratory, Shanghai, China, following the kit's instruction manual. Absorbance readings were conducted on a Chromate 4300 brand ELISA reader device (Awareness Technology, Inc. Martin Hwy. Palm City, USA) at 450 nm, and results were calculated using linear regression.

Statistical analysis

The data acquired from the study underwent analysis using SPSS 22 Software for Windows. The normal distribution of the data was assessed through the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were represented as numbers (percentages), while continuous variables were expressed as "mean ± standard deviation (SD)." Intergroup comparisons for categorical variables were conducted using the Chi-square test, and for continuous variables, one-way ANOVA (post-hoc LSD) was applied. Pearson's r was computed to illustrate the correlation between plasma adiponectin level and other continuous variables.

RESULTS

Table 1 presents the clinical characteristics of participants in the control, AF, and lone AF groups. The average age in both the AF and Lone AF groups was significantly higher compared to the control group (p<0.001 for both). The mean age of the Lone AF group was lower compared to the AF group (p<0.001). Among the participants, 53.8% in the control group, 44.7% in the AF group, and 58.8% in the Lone AF group were male, with no significant difference in gender distribution between the groups (p=0.479). Both the AF and Lone AF groups exhibited higher body mass index (BMI) compared to the control group (p<0.001 for both), with no significant difference in BMI between the AF and Lone AF groups (p=0.108).

In the control group, only 7.7% of participants had hypertension and hypercholesterolemia, and they did not have other comorbidities. For patients in the AF group, AF was accompanied by at least one and at most five more diseases.

Table 1. Clinical characteristics of control, atrial fibrillation, and lone atrial fibrillation groups

	Control (n=26)	AF (n=38)	Lone AF (n=34)	P
Age (years)	44.81 ± 3.11	77.05 ± 7.15 *	51.53 ± 5.08 *#	<0.001
Men (n/%)	14 (53.8)	17 (44.7)	20 (58.8)	0.479
Body mass index (kg/m²)	24.31 ± 3.2	30.84 ± 2.88 *	29.66 ± 3.16 *	<0.001
Smoking (n/%)	14 (53.8)	12 (31.6)	16 (47.1)	0.174
Accompanying diseases				
Hypertension (n/%)	2 (7.7)	38 (100)	-	-
Diabetes mellitus (n/%)	-	32 (84.2)	-	-
Heart failure (n/%)	-	4 (10.5)	-	-
Prior stroke/TIA (n/%)	-	2 (5.3)	-	-
Coronary artery disease (n/%)	-	8 (21.1)	-	-
Hypercholesterolemia (n/%)	2 (7.7)	6 (15.8)	2 (5.9)	-
Ischemic heart disease (n/%)	-	4 (10.5)	-	-
Medications				
Antiarrhythmic agents (n/%)	-	32 (84.2)	22 (64.7)	-
Anticoagulant (n/%)	-	30 (78.9)	8 (23.5)	-
Echocardiography				
Left atrium diameter (mm)	32.46 ± 5.74	43 ± 5.88 *	35.21 ± 3.19 *#	<0.001
LVEF (%)	63.92 ± 3.45	57 ± 9.15 *	60.71 ± 3.81 #	<0.001
LVDS (mm)	31 ± 3.82	32.05 ± 3.77	30.18 ± 4.34	0.141
LVEDD (mm)	46.85 ± 4.12	47.95 ± 3.18	46.47 ± 2.85	0.158
LVPWth (mm)	10.46 ± 0.86	11.68 ± 0.66 *	10.88 ±0.77 *#	<0.001
IVST (mm)	10.62 ± 1.02	12.32 ± 0.93 *	11.12 ± 0.98 *#	<0.001
Biochemistry				
Fasting glucose (mg/dL)	96.77 ± 9.99	137.03 ± 48.84 *	100.29 ± 9.69 #	<0.001
Creatinin (mg/dL)	0.84 ± 0.21	0.99 ± 0.4 *	0.79 ± 0.16 #	0.012
LDL (mg/dL)	103.72 ± 30.47	106.06 ± 28.48	107.55 ± 26.66	0.874
HDL (mg/dL)	40.61 ± 9.18	42.31 ± 10.86	43.65 ± 8.12	0.476
Triglyceride (mg/dL)	173.89 ± 84.56	177.73 ± 110.34	144.41 ± 81.01	0.285
Total cholesterol (mg/dl)	171.21 ± 32.43	168.38 ± 32.49	167.75 ± 30.84	0.909

Continuous variables are presented as mean±SD and analyzed using one-way ANOVA. Categorical variables are presented as numbers (percentages) and analyzed using the Chi-square test. P values <0.05 are indicated in bold. *p<0.05 vs Control. #p<0.05 vs AF. AF: atrial fibrillation, TIA: transient ischemic attack, LVEF (%): left ventricle ejection fraction, LVDS (mm): left ventricular sistolic dimension, LVEDD (mm): left ventricular end-diastolic dimension, LVPWth(mm): left ventricle posterior wall thickness, IVST (mm): interventricular septum thickness, LDL: low density lipoprotein, HDL: high density lipoprotein

All participants in the AF group had hypertension, 84.2% had DM, 10.5% had heart failure, 5.3% had a prior stroke/TIA, 21.1% had CAD, 15.8% had hypercholesterolemia, and 10.5% had ischemic heart disease. In the Lone AF group, no other diseases accompanied AF except hypercholesterolemia (5.9%).

While no antiarrhythmic or anticoagulant drugs were used in the control group, 84.2% of the AF group were using antiarrhythmic drugs, and 78.9% were using anticoagulant drugs. In the Lone AF group, 64.7% of the patients were using antiarrhythmic drugs, and 23.5% were using anticoagulant drugs. (Table 1).

Echocardiography findings indicated significant differences only in left atrium diameter, left ventricular ejection fraction (LVEF),(%), left ventricular posterior wall thickness (LVPWth), and interventricular septal thickness (IVST) among the groups.

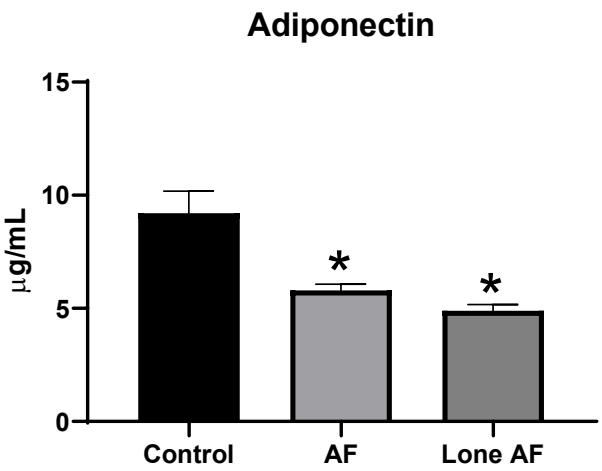

Figure 1. Plasma adiponectin level (µg/mL) of Control, AF and Lone AF groups. Data were presented as mean ± standard deviation (SD). One-way ANOVA (post-hoc LSD) was used for comparisons between groups. *p<0.001 vs control group. AF: atrial fibrillation.

The left atrium diameter increased in both the AF and Lone AF groups compared to the control group (p<0.001, p=0.04, respectively), with a further increase in the AF group compared to Lone AF (p<0.001). LVEF (%) decreased in the AF group compared to both the control and Lone AF groups (p<0.001, p=0.016, respectively). LVEF (%) also showed a lower value in the Lone AF group compared to the control group, though this difference approached borderline significance (p=0.056). Both LVPWth and IVST showed a significant increase in both the AF and Lone AF groups compared to the control group (p<0.001, p=0.035 for LVPWth; p<0.001, p=0.05 for IVST, respectively). Moreover, both LVPWth and IVST showed higher values in the AF group compared to the Lone AF group (p<0.001, p<0.001, respectively), (Table 1).

Biochemical variables, including HDL, LDL, triglycerides, and total cholesterol levels, showed no significant differences across the groups. However, fasting glucose and creatinine levels were higher in the AF group compared to the control group (p<0.001, p=0.048, respectively). Similarly, fasting glucose and creatinine levels were elevated in the AF group compared to the Lone AF group (p<0.001, p=0.004, respectively).

There was no significant difference in adiponectin levels between the AF and Lone AF groups (p=0.191) (Figure 1). The correlation analysis revealed a negative association between adiponectin levels and BMI (r=-0.241, p=0.017) (Figure 2). Additionally, adiponectin showed a positive correlation with LVEF (r=0.208, p=0.04) and a negative correlation with LVPWth and IVST based on echocardiographic data (r=-0.439, p<0.001; r=-0.416, p<0.001, respectively).

DISCUSSION

There remains uncertainty regarding whether the changing plasma adiponectin levels observed in AF patients is a consequence of AF itself or a result of hypertension, diabetes, or cardiac diseases associated with AF. Therefore, the aim of this study was to investigate plasma adiponectin levels in Lone AF patients who do not have any accompanying diseases.

Apart from being one of the most abundant endogenous adipocytokines in the body, adiponectin is recommended as one of the biomarker proteins for prognosis in cardiovascular diseases (12). Plasma levels of adiponectin decrease in diseases such as obesity, type 2 DM, CAD, and hypertension (8). The decrease in adiponectin levels in diseases such as obesity, type 2 DM, CAD, and hypertension, which are included in the etiology of AF and pave the way for the formation of AF, creates an expectation that the level of adiponectin will also decrease in AF. The observation of reduced adiponectin levels in patients with Lone AF and AF, a central finding in our study, is consistent with this anticipation. The study of Assar et al., who pointed out that low adiponectin levels may contribute to postoperative AF, also supports our findings (13). Nevertheless, some studies highlight a substantial association between adiponectin and AF; conversely, they propose that elevated adiponectin levels might pose a risk factor for AF (6, 8-10). To clarify the inconsistency among various studies, it is essential to assess the subtypes of AF.

Following a similar line of thought (8) hoped that plasma adiponectin levels in patients with AF would be lower compared to control patients, but they found high adiponectin levels in patients with persistent AF. On the

other hand, despite high adiponectin in the persistent AF group, they found lower adiponectin levels in paroxysmal AF compared to the control group.

Another group of researchers corroborated the earlier study by demonstrating that serum adiponectin levels were notably elevated in patients with persistent AF compared to those with sinus rhythm, yet significantly lower in patients with paroxysmal AF (14). Perhaps the discrepancy between these two cross-sectional studies (8, 14) and, other studies (6, 8-10) that suggests that high levels of adiponectin in AF may be attributed to the fact that AF was not divided into subtypes such as paroxysmal, permanent, and persistent.

Unfortunately, the AF group could not be subdivided into subtypes due to an insufficient number of patients for statistical analysis. Although the AF group could not be categorized further, the majority (42.1%) of the AF group in our study consisted of patients with paroxysmal AF. Out of the remaining patients, 31.6% had persistent AF, and 26.3% had permanent AF. In this study, it was observed that plasma adiponectin levels were lower in both the AF and Lone AF groups when compared to the control group. There was no significant difference between the AF and Lone AF groups in terms of adiponectin levels. In fact, our results contribute to the literature on the role of adiponectin as follows: Previous studies have demonstrated the relationship between adiponectin levels and AF, but factors predisposing to AF (such as diabetes, hypertension, acute coronary syndrome) could not be excluded. However, the observation that the adiponectin level was lower in the Lone AF group, which was completely free of these variables, compared to the control group, supports the idea that adiponectin decreases due to arrhythmia independently of secondary factors.

In the present study, left atrium size, LVEF, LVPWth, and IVST, which are echocardiographic findings, were found to differ significantly between the groups. The left atrium size, elevated in both the AF and Lone AF groups in comparison to the control group, exhibited a further increase in the AF group when compared to the Lone AF group. Hypervolemia, which increases left ventricular filling pressures in obesity, which is one of the risk factors for AF, leads to left atrial enlargement, which is one of the early signs of left ventricular dysfunction (15). To our knowledge, the relationship between adiponectin and left atrial size in obese patients has not been resolved to date. While one study indicated that adiponectin was negatively correlated with left atrium size (15) another study found a positive correlation (9). However, in this study, no correlation was found between adiponectin level and left atrium dimensions in patients with Lone AF and AF. Low LEVF in atrial fibrillation is considered a left ventricular dysfunction (16).

In this study, LVEF was lower in the AF group compared to the control and Lone AF groups. It was also lower in the Lone AF group compared to the control, but this difference was at a level that could be considered borderline significant. These results align with our rationale for selecting patients with Lone AF. Thamilarasen et al. observed an increase in left atrium size and a decrease in LVEF in patients with Lone AF (17). The increased left atrium dimensions in the Lone AF and AF groups of our study compared to the control group, and especially the decreased LVEF in AF, align with this study. The positive correlation of plasma adiponectin, released from adipose tissue with a favorable cardiovascular profile, with LVEF, and the negative correlation with LVPWth and IVST in our study further supports its characterization as a beneficial adipocytokine. Despite its release from adipose tissue, increased adiposity, especially visceral fat, reduces adiponectin secretion (18).

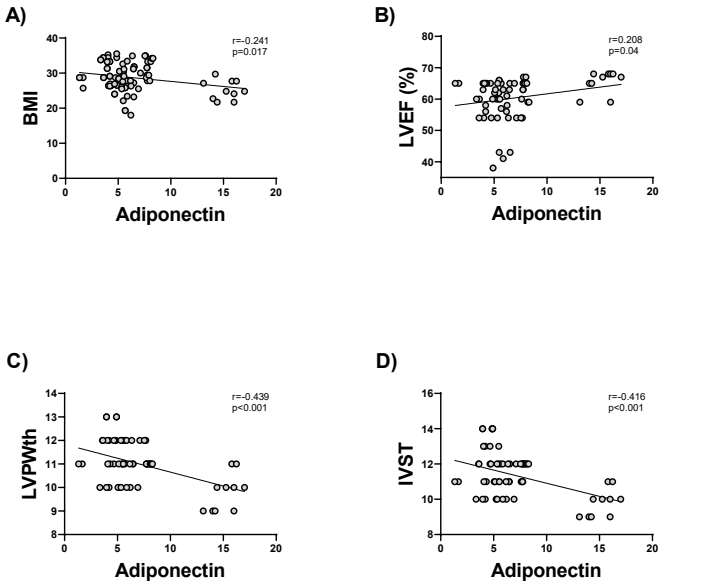

Figure 2. Scatter plots showing the relationship between plasma adiponectin level and body mass index:BMI (A), left ventricular ejection fraction:LEVF (%) (B), left ventricular posterior wall thickness:LVPWth (C), and interventricular septal thickness:IVST (D).

Therefore, circulating adiponectin levels also decrease in obesity due to abdominal adiposity. Studies examining the relationship between BMI and AF suggest that obesity may partially mediate the increased risk of AF but it does not solely contribute to it (6, 9, 19). Moreover, there is a suggestion that obesity could act as a risk factor for Lone AF, underscoring the connection between individuals with Lone AF and elevated BMI (20). Consistent with this study, our research revealed a negative correlation between BMI and adiponectin.

In summary, the current study is the first one to establish the connection between adiponectin and Lone AF. Our results indicate that low adiponectin is independently associated with Lone AF, and this association persists in patients with secondary AF. Consequently, we propose that adiponectin decreases in Lone AF and AF due to arrhythmia independently of secondary diseases.

Limitations of the study

Due to the fact that this study was conducted at a single center and the number of patients was small, patients with AF could not be divided into subgroups.

CONCLUSION

These findings imply that adiponectin levels might contribute to the pathophysiology of arrhythmia. Currently, it remains unclear whether low adiponectin is merely a marker in Lone AF or an active participant in pathogenesis. We anticipate that our findings will guide future studies in unraveling the mechanisms underlying the pathogenesis associated with the relationship between low adiponectin levels and Lone AF.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: All procedures were approved by the Afyonkarahisar Health Sciences University Non-interventional Clinical Studies by the Ethics Committee (Approval number: 2022/428).

Athorship Contributions: Concept: ÖK, AKK, ZY, Design: ÖK, AKK, ZY, Supervision: ÖK, AKK, ZY, Financing and equipment: ÖK, AKK, ZY, Materials: ÖK, AKK, ZY, Data collection and entry: ÖK, AKK, ZY, Analysis and Interpretation: ÖK, AKK, ZY, Literature Search: ÖK, AKK, ZY, Writing: ÖK, AKK, ZY, Critical Review: ÖK, AKK, ZY.

REFERENCES

1. Sawano M. Lone Atrial Fibrillation Reconfirmed as Unfavorable Arrhythmia. J Atheroscler Thromb. 2021;28(3):225-6. doi: 10.5551/jat.ED137. https://doi.org/10.5551/jat.ED137
2. Roston TM, Islam S, Hawkins NM, et al. A Population-Based Study of Unexplained/Lone Atrial Fibrillation: Temporal Trends, Management, and Outcomes. CJC Open. 2021;4(1):65-74. https://doi.org/10.1016/j.cjco.2021.09.006
3. Potpara TS, Lip GHY. Lone atrial fibrillation: what is known and what is to come. Int J Clin Pract. 2011;65(4):446-57. https://doi.org/10.1111/j.1742-1241.2010.02618.x
4. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-20. doi: 10.2147/CLEP.S47385. Available from: https://doi.org/10.2147/CLEP.S47385
5. Frost L, Anderson LV, Godtfredsen J, et al. Age and risk of stroke in atrial fibrillation. Neuroepidemiology. 2007;28(2):109-15. https://doi.org/10.1159/000101509
6. Yamaguchi N, Okumura Y, Watanabe I, et al. Clinical implications of serum adiponectin on progression of atrial fibrillation. JArrhythm. 2017;33(6):608-12. https://doi.org/10.1016/j.joa.2017.07.009
7. Barnett AS, Piccini JP. Adiponectin: an accurate biomarker for patients at risk for atrial fibrillation? Heart. 2015;101(17):1351-2. https://doi.org/10.1136/heartjnl-2015-307816
8. Shimano M, Shibata R, Tsuji Y, et al. Circulating Adiponectin Levels in Patients With Atrial Fibrillation. Circ J. 2008;72(7):1120-4. https://doi.org/10.1253/circj.72.1120
9. Zhu T, Wang Z, Wang S, et al. Association between Serum Adiponectin and Atrial Fibrillation: A Case-Control Study Stratified by Age and Gender. Cardiol Res Pract. 2021;2021:6633948. https://doi.org/10.1155/2021/6633948
10. Guo Y, Liu L, Wang J. Adiponectin and the risk of new-onset atrial fibrillation: a meta-analysis of prospective cohort studies. Biosci Rep. 2019;39(6):BSR20182284. https://doi.org/10.1042/BSR20182284
11. Lin K, Marine JE, Calkins H, et al. Should we abandon the term "lone atrial fibrillation"? Hellenic J Cardiol. 2019;60(4):216-23. https://doi.org/10.1016/j.hjc.2019.04.005
12. Hernández-Romero D, Jover E, Marín F, et al. The prognostic role of adiponectin levels in atrial fibrillation. Eur J Clin Invest. 2013;43(2):168-73. https://doi.org/10.1111/eci.12028
13. Assar O. Low adiponectin level may contribute to higher incidence of post-cardiac surgery atrial fibrillation in obese patients. Ann Thorac Surg. 2012;93(5):1762-3. https://doi.org/10.1016/j.athoracsur.2011.09.025
14. Choi BJ, Heo JH, Choi IS, et al. Hypoadiponectinemia

in patients with paroxysmal atrial fibrillation. Korean Circ J. 2012;42(10):668-73. https://doi.org/10.4070/kcj.2012.42.10.668

15. Ybarra J, Resmini E, Planas F, et al. Relationship between adiponectin and left atrium size in uncomplicated obese patients: adiponectin, a link between fat and heart. Obes Surg. 2009;19(9):1324-32. https://doi.org/10.1007/s11695-009-9924-5
16. Wijesurendra RS, Liu A, Eichhorn C, et al. Lone Atrial Fibrillation Is Associated With Impaired Left Ventricular Energetics That Persists Despite Successful Catheter Ablation. Circulation.2016;134(15):1068-81. https://doi.org/10.1161/CIRCULATIONAHA.116.024679
17. Thamilarasan M, Grimm RA, Rodriguez LL, et al. Left ventricular diastolic dysfunction in lone atrial fibrillation determined by Doppler tissue imaging of mitral annular motion. Am J Cardiol. 2000;86(9):1026-9, A10. https://doi.org/10.1016/s0002-9149(00)01144-9
18. Pahlavani HA. Exercise Therapy for People With Sarcopenic Obesity: Myokines and Adipokines as Effective Actors. Front Endocrinol (Lausanne). 2022;13:811751. https://doi.org/10.3389/fendo.2022.811751
19. Ermakov S, Azarbal F, Stefanick ML, et al. The associations of leptin, adiponectin, and resistin with incident atrial fibrillation in women. Heart. 2016;102(17):1354-62. https://doi.org/10.1136/heartjnl-2015-308927
20. El-Assaad I, Al-Kindi SG, Saarel EV, et al. Lone Pediatric Atrial Fibrillation in the United States: Analysis of Over 1500 Cases. Pediatr Cardiol. 2017;38(5):1004-9. https://doi.org/10.1007/s00246-017-1608-7

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1552447
Interdiscip Med J 2025;16(54):25-32

Effects of vascularization when different alloplastic implant materials are used in adjacently with acellular dermal matrix

Sevin Fariz[1], Meryem Ilkay Karagul[2], Sakir Necat Yilmaz[3], Zehra Demiray Asoglu[2], Merve Turkegun Sengul[4]

[1] Health Sciences University Faculty of Medicine, Adana City Training and Research Hospital, Department of Plastic Reconstructive and Aesthetic Surgery, Adana, Türkiye
[2] Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Histology and Embryology, Hatay, Türkiye
[3] Mersin University Faculty of Medicine, Department of Histology and Embryology, Mersin, Türkiye
[4] Alanya Alaaddin Keykubat University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Antalya, Türkiye

Abstract

Objective: Autologous tissue transplantation is the best way to repair tissue defects. Autologous graft materials can cause in the formation of scars and, in some cases, a reduction in the functionality of the donor site. This study aimed to ascertain how often revascularization in the acellular dermal matrix (ADM) is formed when different types of alloplastic implant materials are used in reconstructions.

Method: The Wistar albino rats were assigned to three groups (n=7): various alloplastic materials (porous polyethylene, titanium, tricalcium phosphate, silicone), coated with ADM, were placed in distinct subcutaneous pockets on the thoracodorsal region of the rats, at 7, 14, and 21 days post-procedure, the rats were sacrificed for sampling. Sections were stained with hematoxylin-eosin. The degree of revascularization was assessed through the use of immunohistochemical labelling (anti-CD105 antibody).

Results: The results indicated that minimal revascularization was observed on day 7, while significantly increased revascularization was evident on days 14 and 21. The use of alloplastic materials showed a significant increase in the number of CD105-positive vessels on days 7, 14 and 21. There was an increase in the number of CD105-positive vessels on day 21 compared to day 7. There was no significant difference in the number of CD105-positive vessels between days 7 and 14 in the tricalcium phosphate and silicone groups.

Conclusion: The study concluded that distinct alloplastic implants used adjacent to ADM have no negative impact on revascularization rates. This is the most sought-after objective in the field of soft tissue reconstruction.

Keywords: Acellular dermal matrix, alloplastic material, vascularization, immunohistochemistry

INTRODUCTION

Biomaterials have been widely used for tissue augmentation in plastic, reconstructive and aesthetic surgery practice (1). The soft tissue covering over the inserted implant must be well vascularized and preferably thick (2). Well-vascularized and thick coverage prevents implant extrusion, visibility, and palpation especially when placed in pockets with thin or insufficient soft tissue coverage (1-4). Well-vascularized tissue coverage also helps prevent infection and perfusion problems. Finding sufficient tissue to cover the implant is sometimes a challenge, such as unreliable and/or inadequate soft tissue or skin due to previous surgery or radiation (4-7).

The concept of covering an alloplastic material with another avascular layer may decrease or prevent revascularization, thus creating a dead space and increasing the risk of infection, which is generally chronic and resistant to antimicrobial treatment. The acellular dermal matrix (ADM) is used for supporting the envelope covering the implant for reconstruction after mastectomy (7-9). ADM can also be used for reconstruction of calvarial bone defects in order to prevent extrusion of the implant (10-12). These instances can be expanded according to many other clinical

Cite this article: Fariz S, Karagul MI, Yilmaz SN, Demiray-Asoglu Z, Turkegun-Sengul M. Effects of vascularization when different alloplastic implant materials are used in adjacently with acellular dermal matrix . Interdiscip Med J. 2025;16(54):25-32. https://doi.org/10.17944/interdiscip.1552447

Corresponding Author: Dr. Meryem Ilkay Karagul, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Histology and Embryology, Hatay, Türkiye
Email: meryemilkay.karagul@mku.edu.tr
ORCID iD: 0000-0002-1990-2640

Received: Sep 19, 2024
Accepted: Feb 8, 2025

scenarios (13-15). Although this type of dual use, "adjacent to alloplastic material" has proven to be successful in the clinical scenario, experimental studies are needed to evaluate the neovascularization behavior of the biological matrix when used adjacent to an alloplastic material (dual use) (12,14).

In this study, it was aimed to determine the vascularization rate/amount of ADM when used adjacent to different kind of alloplastic material [dual use such as; silicone (dimethylsiloxane), ceramic (calcium triphosphate), metal (titanium), polymer (porouspolyethylene)]. It was thought that the revascularization rate/amount over time is an important measure for a complication-free application of dual use of ADM adjacent to alloplastic material.

METHOD

The present study was conducted in accordance with the approval of the Ankara University Animal Experimentations Local Ethics Committee, as evidenced by its decision dated May 22, 2013 and numbered 11/78. Twenty-one male Wistar albino rats weighing between 250-280 g were used in this study. The animals were kept under standard light/dark cycle and temperature and provided with water and standard dry rat food ad libitum.

Surgical procedures

All animals were administered by single intramuscular injection of ketamine HCL (Ketalar, Pfizer Warner Lambert, NY, USA) 1 mg/kg and xylazine (Alfazyne %2, Alfasan, Woerden, Holland) 0.2 mg/kg prior to surgery. After anesthesia, the dorsal region of the rats was shaved and scrubbed with povidone iodine solution.

Four types of implants were prepared prior to surgery;

1) Silicone sheets were prepared from smooth rectangle 15×8 cm expandable implant (Mentor®, Santa Barbara, California, USA) cut with scissors for implantation (1×1 cm flat in size).

2) Titanium plates (Trimed®/Electron Medical, Ankara, Türkiye) were prepared 1×1 cm flat in size.

3) Tricalcium phosphate cement sheets (Arex Bone®, Kasios, France) were prepared 1×1 cm flat in size.

4) Porous polyethylenes (Medpor®/Howmedica Osteonics Corp., Newnan, USA) were prepared 1×1 cm flat in size.

After following step, ADMs, 4×12 cm 0.7-1.7 cm thick (Belladerm/MTF®, Edison, NJ, USA) and rehydrated state, were taken from its package for use and were cut with scissors and sterilely prepared for implantation (1×1 cm flat in size). 1×1 cm in diameter were made on the surface of rat's thoracodorsal region two of them on the left side and three of them on the right side in all groups. Five subcutaneous pockets were created just above the panniculus carnosus. In all groups, dorsal pockets were prepared and implants were inserted adjacent to ADM in four dorsal subcutaneous pockets for the next step. The implants and ADM were not attached or wrapped, they were only inserted adjacently. They were fixed in because of the dorsal pockets's size appropriate. No deformation was observed. The fifth pocket was used as a control and only ADM was inserted. Finally, the incisions were closed with 4/0 polypropylene suture (Prolene®, Ethicon, Pomezia, Italy) (Figure 1). The rats were taken into separate cages to prevent them harming each other. Animals were examined daily by the investigator for wound infection, tissue reaction, haematoma, implant exposure, and bulging. All animals survived after the procedures without complications were related to the implantation sites. Days 7, 14, and 21 were sacrificed by decapitation and the implants and surrounding tissues were removed. Biopsies were harvested by rectangular full thickness way of surrounding and totally integrated tissue around the implants. Implants were removed before sampling. Histological specimens were obtained from ADM located at the anterior surface of the implants inserted subcutaneous tissue below skin.

Histopathological evaluation

Specimens were fixed in 10% neutral buffered formalin solution for 48 hours and prepared for routine histological investigation. Afterwards, the biopsies embedded in paraffin, 4µm thick vertical sections were taken with the help of microtome (Leica ® RM2125RT, Leica Austria-Vienna). The sections were stained with hematoxylin-eosin and they were examined by light microscopy.

Immunohistochemical staining protocol

Tissues were held in 10%-neutral formalin solution (pH:7.4) for 48 hours. Routine light microscopic tissue analysis was carried out for fixed tissues and then they were stored in paraffin-embedded blocks. In order to evaluate the vascularization in the tissues, the sections taken from the blocks were properly stained with anti-CD105 antibody in accordance with the protocol mentioned below. Sections with a thickness of 4 µm were placed over adhesive slides. In order to get rid of fixation and antigen masking caused by embedding in paraffin, they were treated with trypsin (pH:7.6) at 37 °C for 30 minutes (antigen retrieval). They were then washed with phosphate-buffered saline (PBS) 3× for 5 minutes. To block the endogenous peroxidase activity, they were incubated with 12.5% hydrogen peroxide (H2O2) in distilled water for 10 minutes and washed with PBS 3× for 5 minutes. To prevent non-specific antibody binding, they

were incubated with protein block for 8 minutes. The protein block over the tissues was removed away and, without any washing, anti-CD105 rabbit polyclonal primary antibody (Abcam, ab107595), which was diluted 1/200 with 0.5% bovine serum albumin (BSA)was instilled. The sections were incubated overnight at +4 °C. After application of primary antibody, they were washed with PBS 3× for 5 minutes. The polyvalent secondary antibody, which is conjugated with biotin (Abcam, ab93697) was instilled. They were kept at room temperature for 10 minutes and then washed with PBS 3× for 5 minutes. They were incubated with streptavidin peroxidase enzyme solution for 10 minutes and washed with PBS 3× for 5 minutes. Diaminobenzidine, a substrate of peroxidase, was instilled. Counterstaining was carried out with hematoxylin. For negative control, 0.5% PBS-BSA containing no primary antibody was instilled to the sections. Then the protocol was followed in the same way. After the sections were stained, CD105-positive vessels were counted in each of 10 different areas at 400× magnification and the mean density was reported. Sections were photographed with an integrated digital camera of the Olympus BX50 light microscope.

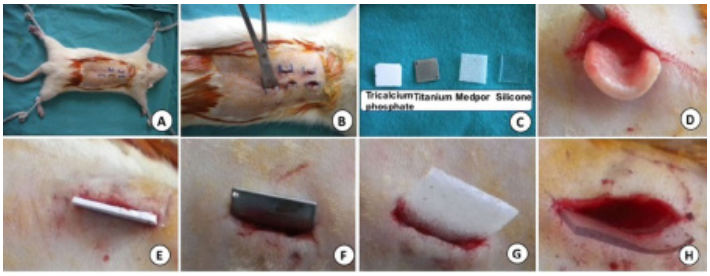

Figure 1. (A, B) Different skin pouches created on thoracodorsal region of the rats. (C) Used different alloplastic implant materials. (D) The ADM, (E) the tricalcium phosphate, (F) the titanium, (G) the metpor, and (H) the silicone was inserted into skin pouche created on the right thoracodorsal region.

Table 1. The number of the CD105-positive vessels in ADM and alloplastic implants on days 7, 14, and 21

Variable	Day 7	Day 14	Day 21	p-value
ADM	410.14±143.62‡	642.14±98.03*,II	787.00±92.95*,‡,§,II	p^b<0.001
Titanium	287.28±83.91	1006.28±118.82*	1198.28±66.73*	
Medpor	448.14±97.99	693.42±187.96*	960.14±161.04*	
TP	715.28±79.61†	876.00±162.81†	1353.42±180.26	
Silicone	577.42±192.59†	782.71±215,06†	1497.57±240.74	
p -value	p^a<0.001			
p-value	p^c <0.0001	p^d =0.002	p^e<0.001	

Data are presented as mean ± SD values. ADM: The acellular dermal matrix. TP: Tricalcium phosphate. p^a: Repeated measures ANOVA's p values to compare main effects of time p^b: Repeated measures ANOVA's p values to compare interaction effects of time and groups $p^{c,d,e}$: p values for One-Way ANOVA test. Statistically significant pair wise comparisons for time after Bonferroni post hoc test. *: Compared to Day 7, †: Compared to Day 21. Statistically significant pair wise comparisons for groups on days after Bonferroni post hoc test; ‡: Compared to Tricalcium phosphate, §: Compared to Silicone; II: Compared to Titanium

Statistical analysis

SPSS v.27 software package was used for all statistical analysis of the data. The Shapiro-Wilk test was used to check the assumption of normality. Numeric variables were summarized with the mean and standard deviation. The CD105-positive vessel numbers of means on different days (7, 14, and 21 days) at implant groups were compared by two-factor ANOVA with repeated measures. Also one-way ANOVA was used to compare between implant groups. For pairwise group comparisons according on the ANOVA results, we used the post hoc Bonferroni test. Error-bar graphs were drawn for numerical variables according to different days and groups. For all analyses, $p<0.05$ was considered as statistically significant.

RESULTS

Histopathological findings

Histopathological examination showed minimal revascularization on day 7, increased revascularization on day 14, and increased vessel proliferation on day 21 (Figure 2). Considering the ADM and alloplastic implants used, the number of vessels was found to be higher on day 21 compared to on days 7 and 14 .

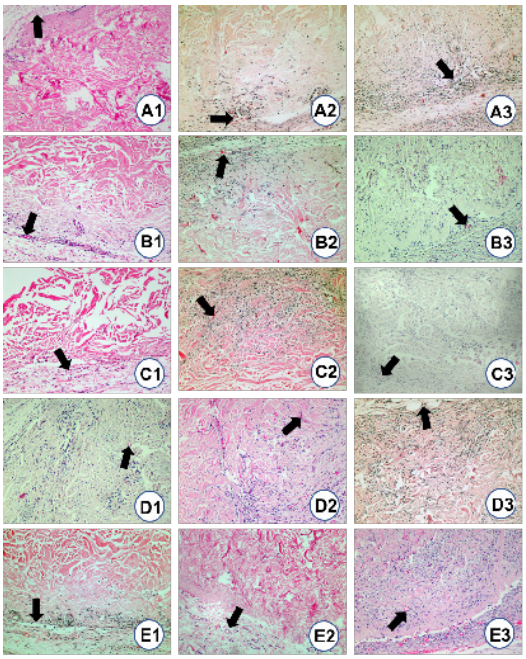

Figure 2. Histological evaluation of the tissue sections. Revascularization is shown on (A1) day 7 ADM, (A2) day 14 ADM, (A3) day 21 ADM, (B1) day 7 silicone, (B2) day 14 silicone, (B3) day 21 silicone, (C1) day 7 medpor, (C2) day 14 medpor, (C3) day 21 medpor, (D1) day 7 tricalcium phosphate, (D2) day 14 tricalcium phosphate, (D3) day 21 tricalcium phosphate, (E1) day 7 titanium, (E2) day 14 titanium, (E3) day 21 titanium. Arrows show blood vessels (H&E stain, All photos magnification 100X).

Immunohistochemical findings

When the evaluation was made without considering the ADM and alloplastic implants used, a statistically significant increase was found in the number of CD105-positive vessels on days 7, 14, and 21 ($p^a<0.001$) (Figures 3, 4, Table 1). Considering the ADM and alloplastic implants used, the number of CD105-positive vessels on days 7th, 14th, and 21st was statistically evaluated. Different alloplastic implants and time were found to affect the vascularization rate ($p^b<0.001$) (Figures 3, 5, Table 1).

The number of CD105-positive vessels in ADM and alloplastic implants was evaluated on days 7, 14, and 21 (respectively; $p^c<0.001$; $p^d=0.002$; $p^c<0.001$) (Figures 3, 5). When compared to ADM on day 7, the number of CD105-positive vessels in the tricalcium phosphate group increased statistically ($p = 0.03$), but there was no significant difference between the other groups ($p > 0.05$) (Figure 5, Table 1). When compared to ADM on day 14, the number of CD105-positive vessels was found to be statistically increased in the titanium group ($p<0.001$) but there was no significant difference between the other groups ($p < 0.05$) (Figure 5, Table 1). When compared to ADM on day 21, the number of CD105-positive vessels was found to be statistically increased in the titanium, tricalcium phosphate and silicone groups, but no significant difference was found with the medpor group (for all groups $p<0.001$ except medpor) (Figure 5, Table 1).

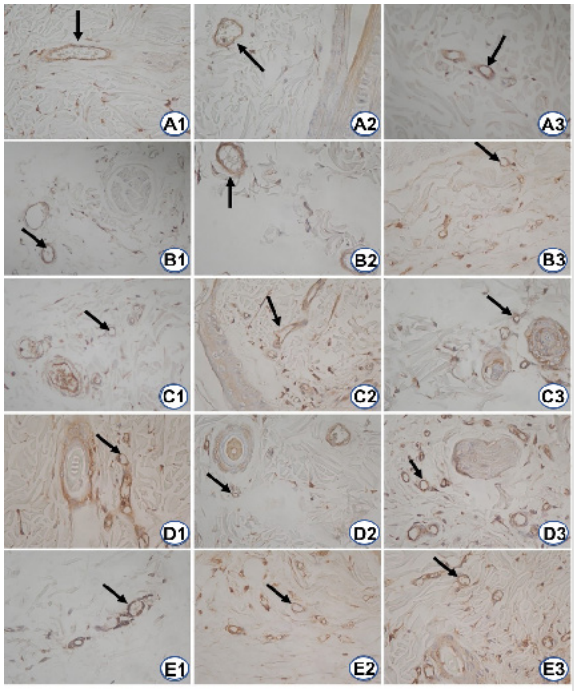

Figure 3. CD105 immunolabeling. Revascularization is shown on (A1) day 7 ADM, (A2) day 14 ADM, (A3) day 21 ADM, (B1) day 7 silicone, (B2) day 14 silicone, (B3) day 21 silicone, (C1) day 7 medpor, (C2) day 14 medpor, (C3) day 21 medpor, (D1) day 7 tricalcium phosphate, (D2) day 14 tricalcium phosphate, (D3) day 21 tricalcium phosphate, (E1) day 7 titanium, (E2) day 14 titanium, (E3) day 21 titanium. Arrows show CD105-positive vessels (All photos magnification 400X).

The mean number of CD105-positive vessels between days in the ADM group showed a statistically significant difference (Figure 5, Table 1). The increase in the number of CD105-positive vessels on days 14, and 21 was statistically significant compared to day 7 in the ADM group (respectively, $p= 0.04$; $p<0.001$) (Figure 4, Table 1). However, when comparing the mean number of CD105 positive vessels on day 14 and day 21 in the ADM group, no statistically significant difference was found ($p > 0.05$) (Figure 5, Table 1). The mean number of CD105-positive vessels between days in all alloplastic implant groups showed a statistically significant difference (Figure 5, Table 1). The increase in the number of CD105-positive vessels on days 14 and 21 was statistically significant compared to day 7 in the titanium and medpor groups (respectively, $p < 0.001$; $p < 0.001$) (Table 1). The increase in the number of CD105-positive vessels on day 21 was statistically significant compared to days 7 and 14 in the tricalcium phosphate and silicone groups (respectively, $p<0.001$; $p<0.001$) (Figure 5, Table 1). However, when the number of CD105 positive vessels was compared between days 7 and 14, no statistically significant difference was found ($p>0.05$) (Table 1).

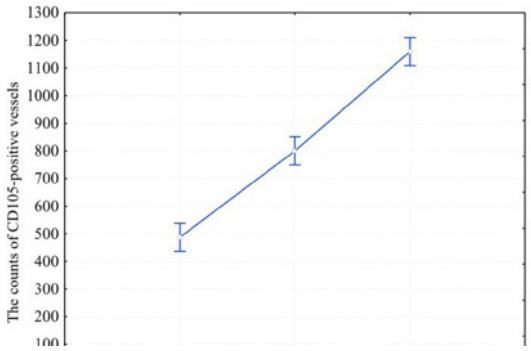

Figure 4. Graphical comparison of CD105-positive vessels counts at days 7, 14 and 21. For Day 7 vs. Day 14 and Day 21, p<0,001; for Day 14 and Day 21, p<0,001 (all p values are for Bonferroni post hoc test after repeated measures ANOVA)

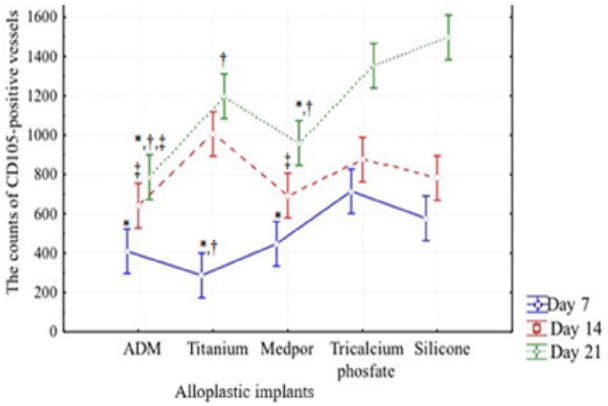

Figure 5. Graphical comparison of the CD105-positive vessels counts of ADM and alloplastic implants (silicone, metpor, tricalcium phosphate, titanium) on days 7, 14 and 21. ADM: The acellular dermal matrix.*: Compared to Tricalcium phosphate; †: Compared to Silicone; ‡: Compared to Titanium. The p-value for the Bonferroni test for all signed pairwise comparisons is <0.05.

DISCUSSION

Allogeneic dermal grafts are used for skin transplantation between genetically disparate individuals of the same species (4,5,16). Acellular allogeneic dermal grafts are derived from human skin of genetically disparate individuals in tissue banks. Donors are evaluated in terms of medical and social aspects in accordance with the United States Food and Drug Administration regulations. All patients undergo serological tests including rapid plasma reagin, venereal disease research laboratory, hepatitis B antigen, human immunodeficiency virus antibody, anti-hepatitis C virus 2 antibody, and anti-human T-lymphotropic virus type 1. Dermal and epidermal cells of the skin grafts are removed to prevent cellular rejection (4). Acellular dermal grafts constitute a suitable ground for the migration, repopulation, and revascularization of the fibroblasts and the endothelial cells of the recipient, thereby, stimulating an improved integration of the ADM with the tissue (6-10,16,17). In addition, ADM has been widely adopted by reconstructive and aesthetic surgeons thanks to its dermal content and biochemical features with low scar contraction in the surgical site. In recent years, these grafts have been used as an additional layer between the prosthesis and the skin to support silicone breast prosthesis in breast reconstruction surgeries (6-10,16-18). Therefore, insertion of these grafts to the adjacent to the alloplastic biomaterials, which can be vascularized, is highly reasonable to prevent extrusion, palpation, or unusual appearance (8,9,16,17). In this study, it was investigated the revascularization pattern of the ADM with implant materials (metpor, tricalcium phosphate, titanium) other than silicone, in which its biological behavior has been well-established to shed light on the scar healing process in different regions of the body.

With the introduction of alloplastic implants in several types of procedures in recent years, studies aiming to prevent material-related complications have been carried out (19,20). In addition, alloplastic implants have been increasingly utilized in the reconstruction of soft tissues and bone defects (21,22). A number of approaches including synthetic, biosynthetic materials, non-absorbable implants, allografts, and cross-linked biological materials have been defined for tissue defect repair. Based on the chemical compositions, implant materials can be classified into four groups including metal alloy implants, ceramic alloy implants, polymers, and biological implants (1-3,23). The main merits of these implants, as an alternative to the autogenous tissue grafts, include shorter surgery time, absence of donor site-related morbidity, and low exposure to resorption (4,5,7). Review of the literature also revealed several studies reporting the use of ADM in the prevention of implant exposure during breast reconstruction with silicone implants (5-9,16,17). In addition, several biomaterials including biological meshes can be used in other regions of the body.

Since there is no published material with comparative data related to the vascularization pattern of the ADM combined with titanium, calcium triphosphate, or porous polyethylene implants in the literature, in the present study, the revascularization process of the ADM was evaluated with implant materials other than silicone, including titanium, calcium triphosphate, and porous polyethylene. One of the early experimental studies on revascularization of ADM was conducted by Eppley (24). In the aforementioned study, the author placed sheet and rolled ADM configurations subcutaneously and evaluated the revascularization pattern. He reported that vascular ingrowth along the implants was slower in the rolled configurations, while revascularization of single-layer acellular human dermis was completed by 14 days following surgery (4). The aim of the present study was to determine the incidence of revascularization in ADM when different types of alloplastic implant materials (porous polyethylene, titanium, tricalcium phosphate, silicone) were used for reconstruction. When the evaluation was made without taking into account the ADM and alloplastic implants used, we found that the number of vessels increased on days 7, 14 and 21. We therefore assumed that the increase in vascularization was time-dependent.

Thakker et al. performed a histological examination of fibrovascular ingrowth within hydroxyapatite and porous polyethylene orbital implants wrapped in ADM (25). Similar to the study findings, the authors reported that ADM wrapping supported vascularization without any acute or chronic inflammation manifestations and prevented outer tissue abrasion. Lin et al. similarly reported that implants which were used in cranial defects in a pediatric population undergoing reconstruction surgery with porous polyethylene were not extruded with a preserved tissue layer and good cosmetic results were obtained (26). Wong et al. used alloplastic materials in the prefabricated inferior epigastric-based flaps in rats (27). The composition of the cellular infiltration into the ADM and the time course of the vascularity process were investigated. The authors concluded that the host response to ADM was parallel with normal wound healing and revascularization was satisfactorily achieved, although the flap was covered with silicone. Ribeiro et al. used two alloplastic materials similar to the ones used in the current study (28). Bone defects were filled with bioactive glass and ADM. They observed a large amount of bone formation on days 10 and 30 postoperatively. Similarly, a statistically significant vascularization was reported on day 21 following the implantation of the alloplastic materials. Taufique et al. demonstrated that ADM used in skull base repair surgery was

revascularized rapidly. They observed that ADM was integrated with the dura. The harvested specimen had new blood vessels, as well as spindle cells, indicating the formation of new vessels within the ADM (29). The results of the current study are also consistent with these findings, indicating high revascularization of ADM. We observed the skin sections under a light microscope and found that the number of vessels increased in the ADM group on days 14 and 21 compared to day 7. At the same time, immunohistochemical findings showed that the increase in revascularization over time was significant in the ADM group. In addition, different alloplastic implant materials (silicone, metpor, tricalcium phosphate and titanium) coated with ADM were placed in different subcutaneous pockets in the thoracodorsal region of rats and the revascularization rate was evaluated immunohistochemically after 7, 14, and 21 days. Compared to ADM, the number of vessels was significantly increased in the tricalcium phosphate group on day 7 and in the titanium group on day 14. On day 21, the number of vessels increased significantly in the titanium, tricalcium phosphate, and silicone groups, while no significant change was observed in the Medpor group. Therefore, we concluded that different alloplastic implant materials (silicone, tricalcium phosphate and titanium) coated with ADM affect vascularization in a time-dependent manner.

Overall, these findings suggest that ADM is not rejected, showing a good invasion rate by the host cells, high vascularization, improved tissue quality, and strong integrity with the tissue. Similarly, the study achieved consistent results, although it was utilized only two avascular materials. These findings also suggest that donor site-related morbidity may be reduced in possible tissue, which demonstrated that ADM had a unilateral vascularization pattern, despite the avascular nature of both avascular and inert alloplastic implants used in combination with avascular ADM. No suture material was utilized in the experimental groups to avoid any adverse effect of inflammation secondary to hypersensitivity. The study found no inflammation and foreign body reaction on the vascularization process.

As in previous studies, the number of vessels and the degree of revascularization were investigated in the present study. Based on the histopathological examination of the tissues following the removal of alloplastic implants, increased vascularity was observed on day 21 compared to days 7 and 14. In this study, a statistically significant difference was found in the number of vessels on day 21 compared to the other groups. This can be attributed to the fact that ADM, placed adjacently, has no impact on the revascularization rate despite distinct molecular characteristics of alloplastic materials.

Limitations of the study

The principal limitation of this study is that dermal collagen fibres could not be adequately evaluated because Masson's trichrome staining could not be performed. Another limitation is the use of CD105 as the only marker.

CONCLUSION

The relatively rapid revascularization of ADM in the in vitro setting is the major component of efficacy in the reconstructive surgery. In particular, reconstruction can be performed with alloplastic implants in previously operated complex scars with radiation therapy exposure. In this study, the results suggest that alloplastic implants can be safely used in the repair of clinical defects, since the adjacency of the implants with ADM has no adverse effect on the vascularization rate. Revascularization, as one of the major components of reconstructive surgery in the repair of tissue defects, is the most wanted goal for soft tissue reconstruction. The study may help us develop new surgical and non-surgical suggestions that would improve wound healing.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: This study was funded by Scientific Research Project Unit of Kırıkkale University with the project number 2013/59

Previously presented: Some part of this study was presented as poster presentation at "15th International Congress of Histochemistry and Cytochemistry" held in Antalya city, entitled as "Effects of revascularization when different alloplastic implant materials are used in adjacently with acellular dermal matrix".

Thesis: This study was prepared by rearrangement of the specialty thesis by Sevin FARİZ, entitled as "Farklı implant materyallerinin asellüler dermal matriks vaskülarizasyonuna etkileri".

Ethical Declaration: Ethical permission was obtained from the Ankara University Animal Experimentations Local Ethics Board for this study with date May 22, 2013 and number 11/78.

Athorship Contributions: Concept: SF, MIK; Design: SF, MIK; Supervision: SF, MIK, SNY; Financing and equipment: SF, MIK, SNY; Materials: SF, MIK, SNY, ZDA, MTS; Data collection and entry: SF, MIK, SNY, ZDA, MTS; Analysis and Interpretation: SF, MIK, SNY, ZDA, MTS; Literature Search: SF, MIK, SNY; Writing: SF, MIK, SNY, ZDA, MTS; Critical Review: SF, MIK, SNY, ZDA, MTS.

REFERENCES

1. Butler CE, King TW. Implants and Biomaterials In: Neligan PC, editor. Plastic Surgery. Principles. Philadelphia, PA: Saunders Elsevier; 2018. p. 595-604.
2. Atagi TA, Young LV. Alloplastic Materials. In: Mathes SJ, editor. Plastic Surgery. General Principles. Philadelphia, PA: Saunders Elsevier; 2006. p. 745-768.
3. King TW. Implant Materials. In: Grabb and Smith Thorne CH. editors. Plastic Surgery. General Principles. Philadelphia, PA: Lipincott-Williams and Wilkins, Walters Kluver Business; 2014; 64-69.
4. Eppley BL. Experimental assessment of the revascularization of acellular human dermis for soft -tissue augmentation. Plast Reconstr Surg. 2001;107(3):757-62. https://doi.org/10.1097/00006534-200103000-00016
5. Nguyen TJ, Carey JN, Wong AK. Use of human acellular dermal matrix in implant based breast reconstruction: Evaluating the evidence. J Plast Reconstr Aesthet Surg. 2011;64(12):1553-61. https://doi.org/10.1016/j.bjps.2011.02.001
6. Haddock N, Levine J. Breast reconstruction with implants, tissue expanders and Alloderm: predicting volume and maximizing the skin envelope in skin sparing mastectomies. Breast J. 2010;16(1):14-19. https://doi.org/10.1111/j.1524-4741.2009.00866.x
7. Nahabedian MY. AlloDerm performance in the setting of prosthetic breast surgery, infection, and irradiation. Plast Reconstr Surg. 2009;124(6):1743-53. https://doi.org/10.1097/PRS.0b013e3181bf8087
8. Rawlani V, Buck DW 2nd, Johnson SA, Heyer KS, Kim JYS. Tissue expander breast reconstruction using prehydrated human acellular dermis. Ann Plast Surg. 2011;66(6):593-7. https://doi.org/10.1097/SAP.0b013e3181f3ed0a
9. Davila AA, Seth AK, Wang E, Hanwright P, Bilimoria K, Fine N, et al. Human Acellular Dermis versus Submuscular Tissue Expander Breast Reconstruction: A Multivariate Analysis of Short-Term Complications. Arch Plast Surg. 2013;40(1):19-27. https://doi.org/10.5999/aps.2013.40.1.19
10. Hultman SC, Craft CM. Complex Abdominal Wall Reconstruction with Acellular Dermal Matrix. Operative Techniques in General Surg. 2006;8(4):207-15. https://doi.org/10.1053/j.optechgensurg.2006.11.005
11. Lin HJ, Spoerke N, Deveney C, Martindale R. Reconstruction of complex abdominal wall hernias using acellular human dermal matrix: a single institution experience. Am J Surg. 2009;197(5):599-603. https://doi.org/10.1016/j.amjsurg.2008.12.022
12. Janis JE, O'Neill AC, Ahmad J, Zhong T, Hofer SOP. Acellular Dermal Matrices in Abdominal Wall Reconstruction: A Systematic Review of the Current Evidence. Plast And Reconst Surg. 2012;130(5S-2):183-93. https://doi.org/10.1097/PRS.0b013e3182605cfc
13. Silverman RP. Acellular dermal matrix in abdominal wall reconstruction. Aesthet Surg J. 2011;31(7 Suppl):24-9. https://doi.org/10.1177/1090820X11418090
14. Legan M. New Marker of Angiogenesis CD105 (Endoglin): Diagnostic, Prognostic and Therapeutic Role. Radiol Oncol. 2005;39(4):253-9.
15. Yao Y, Kubota T, Takeuchi H, Sato K. Prognostic Significance of Microvessel Density Determined by an Anti-CD105/endoglin Monoclonal Antibody in Astrocytic Tumors: Comparison with an Anti-CD31 Monoclonal Antibody. Neuropathology. 2005;25(3):201-6. https://doi.org/10.1111/j.1440-1789.2005.00632.x
16. Gabriel A, Maxwell GP. Evolving Role of Alloderm in Breast Surgery. Plast Surg Nurs. 2011;31(4):141-50. https://doi.org/10.1097/PSN.0b013e31823b2c30
17. Sbitany H, Serletti JM. Acellular dermis-assisted prosthetic breast reconstruction: a systematic and critical review of efficacy and associated morbidity. Plast Reconstr Surg. 2011;128(6):1162-9. https://doi.org/10.1097/PRS.0b013e318230c29e
18. Margulies IG, Salzberg CA. The use of acellular dermal matrix in breast reconstruction: evolution of techniques over 2 decades. Gland Surgery. 2019;8(1). https://doi.org/10.21037/gs.2018.10.05
19. Ionita S, Popescu S, Lascar I. Polypropylene meshes and other alloplastic implants for soft tissue and cartilage nasal reconstructive surgery – a literature review. Romanian Journal of Rhinology. 2015;5(18):87-94. https://doi.org/10.1515/rjr-2015-0010
20. Ashfaq R, Kovács A, Berkó S, Budai-Szűcs M. Developments in Alloplastic Bone Grafts and Barrier Membrane Biomaterials for Periodontal Guided Tissue and Bone Regeneration Therapy. Int J Mol Sci. 2024;25(14):7746. https://doi.org/10.3390/ijms25147746
21. Laçin N, İzol BS, Gökalp Özkorkmaz E, Deveci B, Deveci E. Effects of alloplastic graft material combined with a topical ozone application on calvarial bone defects in

rats. Folia Morphol. 2020;79(3):528-547. https://doi.org/10.5603/FM.a2019.0101

22. Thoma DS, Gil A, Hämmerle CHF, Jung RE. Management and prevention of soft tissue complications in implant dentistry. Periodontol 2000. 2022;88(1):116-129. https://doi.org/10.1111/prd.12415

23. S AD, P SPA, Naveen J, Khan T, Khahro SH. Advancement in biomedical implant materials-a mini review. Front Bioeng Biotechnol. 2024;12:1400918. https://doi.org/10.3389/fbioe.2024.1400918

24. Eppley BL. Revascularization of Acellular Human Dermis (Alloderm) in Subcutaneus Implantation. Aesthet Surg J. 2000;20(4):291-5. https://doi.org/10.1067/maj.2000.109553

25. Thakker MM, Fay AM, Pieroth L, Rubin P. Fibrovascular ingrowth into hydroxyapatite and porous polyethylene orbital implants wrapped with acellular dermis. Ophthal Plast Reconstr Surg. 2004;20(5):368-73.

26. Lin AY, Kinsella CR Jr, Rottgers SA, Smith DM, Grunwaldt LJ, Cooper GM, et al. Custom porous porethylene implants for large-scale pediatric skull reconstruction: early outcomes. J Craniofac Surg. 2012;23(1):67-70.

27. Wong AK, Schonmayer BH, Singh P, Carlson DL, Li SMS, Mehrara BJ. Histologic analysis of angiogenesis and lymphangiogenesis in acellular human dermis. Plast Reconstr Surg. 2008;121(4):1144-52. https://doi.org/10.1097/01.prs.0000302505.43942.07

28. Ribeiro LLG, Bosco AF, Nagata MJH, de Melo LG. Influence of bioactive glass and/or acellular dermal matrix on bone healing of surgically created defects in rat tibia: a histological and histometric study. Int J Oral Maxillofac Implants. 2008;23(5):811-7.

29. Taufique ZM, Bhatt N, Zagzag D, Lebowitz RA, Lieberman SM. Revascularization of AlloDerm Used during Endoscopic Skull Base Surgery. J Neurol Surg B Skull Base. 2019;80(1):46-50. https://doi.org/10.1055/s-0038-1666851

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1602933
Interdiscip Med J 2025;16(54):33-37

The role of cervical length measurement in predicting the need for hysterectomy in patients with placenta previa

Elif Tiryaki, Kenan Serdar Dolapçıoğlu, Ahmet Beyazıt, Oya Soylu Karapınar

Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Gynecology and Obstetrics, Hatay, Türkiye

Abstract

Objective: To determine the association of cervical length with the need for peripartum hysterectomy in patients with placenta previa
Method: Patients with placenta previa totalis, which performed in 2021, were included in the study. Cervical length was measured by transvaginal technique after 28 weeks. ROC analysis was performed for the cervical length variable in patients requiring peripartum hysterectomy.
Results: Peripartum hysterectomy was performed in 26 out of 66 patients (39.4%). When ROC analysis was performed for cervical length in these patients, AUC was 0.999 (95% confidence interval 0.994-0.999) when the cut-off point was ≤26.5.
Conclusion: The risk of peripartum hysterectomy increases as cervical length shortens.
Keywords: Placenta previa, Cervical length, Peripartum hysterectomy

INTRODUCTION

Placenta previa refers to the abnormal placement of the placenta in the uterus where the placenta closes the cervical canal (1). The risk of placenta previa increases with the number of previous cesarean sections. Recently, it has been encountering more patients with previa due to the uncontrolled increase in the number of cesarean sections. Currently, the incidence is 1 in 200 pregnant women (2). In addition to causing preterm deliveries by causing severe antepartum bleeding, massive uncontrolled bleeding in previa surgeries may lead to hysterectomies and even maternal mortality (3). The need for hysterectomy is 33.26 times higher in patients with placenta previa than in patients with normally located placentas (4). Predicting which patients will require hysterectomy is important in order to be more prepared for cesarean sections. Various ultrasound parameters are used for this purpose. In this study, it was aimed to evaluate cervical length measurement, which is one of these parameters.

METHOD

The study was conducted prospectively in patients with a diagnosis of placenta previa delivered between January 2021 and December 2021 in the Gynecology and Obstetrics Clinic, Mustafa Kemal University Faculty of Medicine. Approval was obtained from the ethics committee of the university (decision number 09 dated 05.02.2021). Informed consent was obtained from all patients and the study was conducted in accordance with the Declaration of Helsinki.

Patients diagnosed with placenta previa totalis by transvaginal ultrasound after 28 weeks of gestation were included in the study. Cervical length measurement was performed by a single specialist physician using a Voluson 730 (Voluson 730, GEMS Kretz UltrasoundV R, Zipf/ Austria) ultrasound device with the standard technique defined by the National Institute of Child Health and Human Development, Maternal-Fetal Network (5).

Patients were asked to empty their bladder before the ultrasound. The vaginal probe was covered with a sterile

Cite this article: Tiryaki E, Dolapçıoğlu KS, Beyazıt A, Soylu-Karapınar O. The role of cervical length measurement in predicting the need for hysterectomy in patients with placenta previa. Interdiscip Med J. 2025;16(54):33-37. https://doi.org/10.17944/interdiscip.1602933

Corresponding Author: Dr. Ahmet Beyazıt, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Gynecology and Obstetrics, Hatay, Türkiye
Email: beyazitahmet@hotmail.com
ORCID iD: 0000-0001-5517-9624

Received: Dec 17, 2024
Accepted: Mar 11, 2025

condom and the distance between the internal os and external os of the cervix was measured three times in the sagittal section and the shortest distance was recorded. If there was funneling, the funnel was excluded and the distance between the tip of the funnel and the external os was measured.

Obstetric history and demographic data were recorded. All patients were delivered by the cesarean section. Artery ligation during cesarean section (hypogastric and/or uterine artery), peripartum hysterectomy status and transfusion amount during hospitalization were recorded.

Pregnant women with partial previa or inferior placenta, multiple pregnancies, pregnancies less than 28 weeks gestation, pregnant women who underwent cerclage or cervical excision procedures and pregnant women with abnormal amniotic fluid index were excluded

Statistical analysis

IBM SPSS Statistics 21.0 (IBM Corp, Armonk, NY, USA) program was used for statistical analysis. Mean±Standard Deviation values were used for descriptive data. Number (n) and percentage (%) values were used to show demographic characteristics. Receiver Operating Characteristic (ROC) analysis was performed for the cervical length variable, which is clinically predicted to be effective in determining the risky group, with reference to patients who underwent peripartum hysterectomy, and ROC graph was drawn, area under the curve (AUC) and 95% confidence intervals of this area were determined.

RESULTS

Between January 2021 and December 2021, 66 patients with a diagnosis of placenta previa totalis were performed by the cesarean section. The mean age was 31.6±4.9 years, the mean number of pregnancies was 4.7±1.8 (min:2-max:13) and the mean number of deliveries was 2.8±1.3 (min:0-max:8). One patient was nulliparous, and 55 (83.3%) patients had a history of previous cesarean section. Demographic and obstetric data of the patients are given in Table 1.

Placenta previa totalis was diagnosed by transvaginal ultrasound in all patients. The mean cervical length at this time was 29.2±5.6 cm. All patients were delivered by cesarean section. The mean gestational age at delivery was 35.5±1.7 weeks.

In our clinic, our approach in placenta previa surgeries is primarily in favor of organ-sparing surgery. For bleeding control, uterine arteries and/or hypogastric arteries are ligated. Arterial ligation was necessary in 41 of patients (62.1%). Peripartum hysterectomy was performed in 26 (39.4%) patients in whom bleeding control could not be achieved. Bladder perforation occurred in 5 (7.6%) patients and bowel serosa damage occurred in 2 (3%) patients in relation to surgery and was recognized perop and necessary procedures were performed. Patients received a mean of 1.6±1.8 (min:0, max:7) units of blood transfusion during hospitalization. Surgical-related data are presented in Table 2.

The ROC curve was drawn for the power of cervical length in determining the need for peripartum hysterectomy. In the analysis, the area under the curve (AUC) was 0.99 when the cut-off point was taken as ≤26.5 mm. The relevant table and ROC curve are given in Table 3 and Figure 1.

DISCUSSION

Placenta previa surgeries are an important reason for peripartum hysterectomies because they can cause massive obstetric bleeding. In this case, an important condition to reduce morbidity and mortality is to decide which patients will require hysterectomy preoperatively and to refer them to a multidisciplinary center and to perform surgery in these centers by taking precautions for both blood preparation and surgical-anesthesia team (6). Ultrasound findings such as the presence of lacunes, thinning of the myometrium in the retroplacental area, and bridge vessels between the placenta and myometrium are among the ultrasound findings indicating that the possibility of bleeding during cesarean section is high and hysterectomy may be required (7).

Cervical length measurement is an ultrasound parameter that has been extensively studied especially in terms of predicting preterm delivery. Measurement of cervical length is a recommended approach, especially in patients with a risk of preterm delivery (5). Because of theories that antepartum bleeding in patients with placenta previa may be the result of cervical effacement, there are studies in which cervical shortening is associated with unfavorable obstetric outcomes in patients with previa (8). Based on these studies, it was aimed to investigate the role of cervical shortening in the prediction of emergency peripartum hysterectomy.

In this study it was found that a short cervix is a risk factor for peripartum hysterectomy in pregnant women with placenta previa. 26 (39.4%) patients required peripartum hysterectomy. Cervical length measurement may be valuable in predicting these patients and according to this study, it can be said that 26.5 mm measurement is the most appropriate value in terms of hysterectomy prediction. In a similar study, it was found that a short cervix was a risk factor for peripartum hysterectomy by Mimura et al. It is recommended that 25 mm is the most appropriate cut-off point by Mimura (9).

Table 1. Demographic and obstetric data of patients

		n (66)	%
Age		31.6±4.9	
Gravity	2	2	3%
	3	17	25.8%
	4	14	21.2%
	5	13	19.7%
	6	11	16.7%
	7	5	7.6%
	8	2	3%
	9	1	1.5%
	13	1	1.5%
Parity	0	1	1.5%
	1	4	6.1%
	2	25	37.9%
	3	17	25.8%
	4	12	18.2%
	5	6	9%
	8	1	1.5%
Mode of delivery	Nullipar	1	1.5%
	Only Vaginal	10	15%
	Only Sectio	45	68.5%
	Vaginal+Sectio	10	15%
Prior section number	0	11	16.7%
	1	4	6.1%
	2	21	31.8%
	3	20	30.3%
	4	7	10.6%
	5	3	4.5%

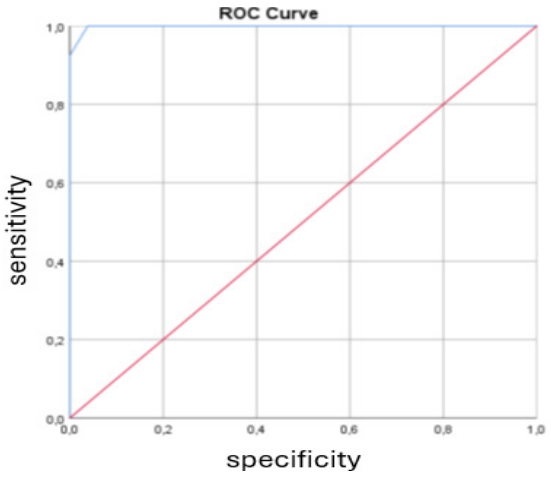

Figure 1. Receiver operating characteristic (ROC) curve of cervical length

Table 2. Surgery-related data

		n:66	%
Pregnancy week at labor		35.5±1.7	
Cervical length (mm)		29.2±5.6	
Blood transfusion (unity)	0	25	37.9%
	1	15	22.7%
	2	11	16.7%
	3	3	4.5%
	4	4	6.1%
	5	6	9.1%
	7	2	3%
Artery ligation	Yes	41	62.1%
	No	25	37.9%
Peripartum hysterectomy	Yes	26	39.4%
	No	40	60.6%
Complication	None	59	89.4%
	Bladder perforation	5	7.6%
	Bowel injury	2	3%

Table 3. Detection power of cervical length for peripartum hysterectomy

Variables	AUC±SD	%95 CI	Cut-off point (cm)	p	Spesifity (%)	Sensitivity (%)
Cervical Length	0.999± 0.002	0.994-0.999	≤26.5	<0.001	99.9	96.2

Abbreviations: AUC: The area under the ROC curve, SD: Standard deviation, CI: Confidence interval

When we look at the literature, there are studies associating cervical shortness with antepartum bleeding in patients with placenta previa. Hessami et al. in their meta-analysis, a shortened cervix was associated with antepartum hemorrhages and an increased risk of preterm delivery due to these hemorrhages (8). However, there was heterogeneity in the studies in this meta-analysis and the cut-off point for the short cervix was taken as 30 mm in some studies and 25 mm in others. When we ignore this heterogeneity, In a multicenter study by Dang et al. cervical length was divided into 4 groups (<2 cm, 2-2.5 cm, 2.5-3 cm, > 3 cm) and it was found that the rate of severe postpartum bleeding and hysterectomy increased as the cervix shortened (10).

Zheng et al. in his study, it was found that antenatal bleeding, emergency cesarean delivery, postpartum bleeding and the need for blood transfusion increased in previa patients with a cervix length shorter than 30 mm (11). Similar to other studies, this suggested that short cervix length is associated with adverse pregnancy outcomes. In a study performed with

MR imaging, it was similarly found that cervical length below 30 mm was associated with adverse pregnancy outcomes (12).

The uterus is structurally weaker than the myometrium in the lower segment. This causes an increase in the amount of bleeding due to inadequate contractions in this region after delivery. In cases of placenta previa, after the placenta located on the cervix is detached at birth, bleeding may be observed from the cervix due to insufficient contraction of the vessels that remain open. In short cervixes, the lower segment becomes wider and longer due to retraction (9). It may be attributed that the need for hysterectomy in patients with a short cervix to the lengthening of the lower segment.

Surgical complications were observed in seven patients in this study. All of these complications were in the group of patients who underwent hysterectomy. Hysterectomy in patients with short cervix is thought to be associated with increased complications. Bladder dissection, clamping and ligating the lateral and medial vascular peduncles, dissection of the pararectal and paravesical spaces, and freeing the ureter are technically more difficult in patients with short cervix (13).

Limitations of the study

This study has some limitations. Heterogeneity among patients is one of them. Another limitation is that there is no distinction between elective and emergency cesarean sections. Emergency cesarean sections performed for antenatal bleeding may have been more liberal in terms of hysterectomy. However, a single cervical measurement was performed. Because of the possibility that the cervical length may have shortened after contractions, serial measurements would be more appropriate.

CONCLUSION

Shortened cervical length is associated with increased peripartum hysterectomy in patients with placenta previa. The Maternal-Fetal Medicine Society does not recommend routine cervical length measurement in patients with placenta previa (14). However, measurement of cervical length with a simple uncomplicated technique on transvaginal ultrasound performed in the antepartum period is valuable in clinical decision-making and informing the patient in terms of showing both preterm delivery due to antenatal bleeding and the risk of peripartum hysterectomy in patients with placenta previa. In this respect, its routine use in patients with placenta previa will be beneficial.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: This study was supported by Mustafa Kemal University Scientific Research Projects Unit (21.TU.005).

Thesis: This study was prepared by rearrangement of the specialty thesis by Elif Nedime Tiryaki, entitled as “plasenta previali hastalarda servikal uzunluk ölçümü ile histerektomi ihtiyacini öngörmedeki rolü”.

Ethical Declaration: Ethical permission was obtained from the Hatay Mustafa Kemal University, Clinical Ethics Committee for this study with date 05/02/2021 and number 09, and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions: Concept: ENT, KSD; Design: ENT, KSD; Supervising: KSD; Financing and equipment: ENT, KSD, OSK; Data collection and entry: ENT, KSD; Analysis and interpretation: ENT, KSD; Literature search: AB; Writing: AB; Critical review: AB, KSD

REFERENCES

1. Jauniaux E, Bhide A. Prenatal ultrasound diagnosis and outcome of placenta previa accreta after cesarean delivery: a systematic review and meta-analysis. Am J Obstet Gynecol. 2017;217(1):27-36. http://doi:10.1016/j.ajog.2017.02.050
2. Cresswell JA, Ronsmans C, Calvert C, Filippi V. Prevalence of placenta praevia by world region: a systematic review and meta-analysis. Trop Med Int Health. 2013;18(6):712-24. http://doi:10.1111/tmi.12100
3. Mitsuzuka K, Togo A, Nakajima R, Kanno Y, Sato K, Ishimoto H. Is Cervical Length a Useful Predictor of Antepartum Hemorrhage in Patients with Placenta Previa?. Tokai J Exp Clin Med. 2022;47(4):204-8.
4. Crane JM, Van den Hof MC, Dodds L, Armson BA, Liston R. Maternal complications with placenta previa. Am J Perinatol. 2000;17(2):101-5. http://doi:10.1055/s-2000-9269
5. Iams JD, Goldenberg RL, Meis PJ, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996;334(9):567-72. http://doi:10.1056/NEJM199602293340904
6. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol. 2006;107(6):1226-32. http://doi:10.1097/01.AOG.0000219750.79480.84

7. Califano G, Saccone G, Maria Maruotti G, et al. Prenatal identification of invasive placentation using ultrasound in women with placenta previa and prior cesarean delivery. Eur J Obstet Gynecol Reprod Biol. 2024;302:97-103. http://doi:10.1016/j.ejogrb.2024.08.035

8. Hessami K, Mitts M, Zargarzadeh N, Jamali M, Berghella V, Shamshirsaz AA. Ultrasonographic cervical length assessment in pregnancies with placenta previa and risk of perinatal adverse outcomes: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2024;6(5S):101172. http://doi:10.1016/j.ajogmf.2023.101172

9. Mimura T, Hasegawa J, Nakamura M, et al. Correlation between the cervical length and the amount of bleeding during cesarean section in placenta previa. J Obstet Gynaecol Res. 2011;37(7):830-5. http://doi:10.1111/j.1447-0756.2010.01446.x

10. Dang X, Fan C, Cui F, et al. Interactions between ultrasonographic cervical length and placenta accreta spectrum on severe postpartum hemorrhage in women with placenta previa. Int J Gynaecol Obstet. 2023;161(3):1069-74. http://doi:10.1002/ijgo.14641

11. Zheng X, Li T, Zeng M, Cheng X, Rao H. The clinical value of prenatal assessment of cervical length and placental thickness in pregnant women with placenta previa. Am J Transl Res. 2021;13(5):5308-14.

12. Zhou L, Zhao X, Xu D, et al. Placental Area in the Lower Uterine Segment, Cervical Length, and Clinical Outcome in Pregnancies With Complete Placenta Previa. J Magn Reson Imaging. 2023;58(4):1047-54. http://doi:10.1002/jmri.28617

13. Polat M, Kahramanoglu I, Senol T, Ozkaya E, Karateke A. Shorter the cervix, more difficult the placenta percreta operations. J Matern Fetal Neonatal Med. 2016;29(14):2327-31. http://doi:10.3109/14767058.2015.1085017

14. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, McIntosh J, Feltovich H, Berghella V, Manuck T. The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. Am J Obstet Gynecol. 2016;215(3):B2-B7. http://doi:10.1016/j.ajog.2016.04.027

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1503687
Interdiscip Med J 2025;16(54):38-44

Inflammatory indices as an indicator of acute pancreatitis severity

Muhammed Fuad Uslu[1], Esra Suay Timurkaan[1], Mustafa Timurkaan[1], Mustafa Yilmaz[2]

[1]Elazig Fethi Sekin City Hospital, Department of Internal Medicine, Elazig, Türkiye
[2]Firat University Faculty of Medicine, Department of Emergency Medicine, Elazig, Türkiye

Abstract

Objective: The present study aimed to compare C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), neutrophil/albumin ratio (NAR), platelet/leukocyte ratio (PLR), systemic immune inflammation (SII), systemic inflammation response index (SIRI) and Ranson criteria associated with inflammation in acute pancreatitis (AP). Thus, the study aimed to analyze the significance ranking of these parameters in terms of disease severity.

Method: The present retrospective study was conducted after the ethics committee approval was obtained. The study included 221 AP patients visited hospital between 01.01.2018 and 31.12.2023. The patients were categorized into two groups based on Ranson criteria: Group 1 (Ranson≤2, n=147) and Group 2 (Ranson≥3, n=74). Basic participant demographics, laboratory reports, CRP, NLR, NAR, PLR, SII, SIRI and hospitalization periods were recorded in a data form, and the findings were analyzed.

Results: There was no difference between the groups based on gender (p=0.094). The Group 2 patients were older (p<0.001) than the ones in Group 1. Furthermore, CRP (p=0.001), NLR (p<0.001), NAR (p<0.001), PLR (p<0.001), SII (p<0.001) and SIRI (p<0.001) were higher in Group 2 patients when compared to Group 1. Also, the hospitalization period was significantly longer in Group 2 (p<0.001) compared to Group 1.

Conclusion: In the study, it was determined that the CRP, NAR, PLR, NLR, SII and SIRI findings were significantly higher in AP patients with a Ranson criteria ≥ 3, and a positive correlation was found between Ranson criteria and inflammatory parameters.

Keywords: Acute pancreatitis, systemic immune inflammation, systemic inflammation response index, hematological parameters

INTRODUCTION

Although the pathogenesis of acute pancreatitis (AP) is multifactorial, pancreatic enzyme activation plays a key role in local pancreatic damage. Based on the severity of inflammation induced by enzyme activation, the pathology of the disease can range between local peripancreatic edema to severe hemorrhagic gangrene and necrosis (1,2).

Early detection of AP severity is important to provide curative treatment and early identification of potential complications. Although various scoring systems have been developed, studies focusing on seeking more practical and result-oriented laboratory parameters continue to increase in the literature.

Previous studies reported that inflammation markers neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios could be employed as prognostic factors in several diseases (SLE, infections, rheumatic diseases, etc.), including certain types of cancer (3-5). Recently, the neutrophil/albumin ratio (NPAR), an inflammatory parameter calculated by dividing the neutrophil ratio by serum albumin concentration, was considered as an inflammatory prognostic factor in several diseases (6-8). However, there is no sufficient evidence on the prognostic value of Neutrophil / Albumin Ratio (NAR) in AP.

Systemic immune inflammation (SII) and systemic inflammation response index (SIRI) are integrated inflammatory biomarkers that could demonstrate local immune response and systemic inflammation throughout the human body (9,10). A recent study examined the predictive value of SII in severe acute pancreatitis and showed that patients with SII values above 1660.36 were more likely to develop severe acute pancreatitis. In another study, the power of SII in the diagnosis of acute pancreatitis was examined and

Cite this article: Uslu MF. Suay-Timurkaan E, Timurkaan M, Yilmaz M. Inflammatory indices as an indicator of acute pancreatitis severity. Interdiscip Med J. 2025;16(54):38-44. https://doi.org/10.17944/interdiscip.1503687

Corresponding Author: Dr. Muhammed Fuat Uslu, Elazig Fethi Sekin City Hospital, Department of Internal Medicine, Elazig, Türkiye
Email: dr.fuslu@gmail.com
ORCID iD: 0000-0001-6300-5130

Received: Jun 23, 2024
Accepted: Mar 16, 2025

it was shown that SII could be used in the diagnosis of acute pancreatitis with 78.7% sensitivity and 46% specificity. (11,12).

Hematological indices have been employed in several studies in recent years due to their non-invasive, rapid, low cost, high sensitivity properties. The present study aimed to investigate the impact of inflammatory parameters during the initial hospitalization of AP patients on disease severity and the duration of hospitalization.

METHOD

For the study, ethical permission was received from the Fırat University Non-Interventional Research Ethics Committee, dated March 05, 2024 and numbered 2024/04-16. The study included the clinical records of 221 AP patients who visited the hospital between 01.01.2018 and 31.12.2023 and fit the inclusion criteria (Figure 1). The patients were categorized into two groups based on Ranson criteria: Group 1 (Ranson≤2, n=147) and Group 2 (Ranson≥3, n=74). Basic participant demographics, laboratory reports, C-reactive protein (CRP), neutrophil/lymphocyte ratio (NLR), neutrophil/albumin ratio (NAR), platelet to leukocyte ratio (PLR), systemic immune inflammation (SII), and systemic inflammation response index (SIRI) and hospitalization periods were recorded in a data form, and the findings were analyzed. AP was diagnosed based on the presence of at least two of the following three criteria: (i) abdominal pain consistent with the disease, (ii) biochemical evidence of pancreatitis (serum amylase and/or lipase level more than three times the upper limit), and (iii) characteristic abdominal imaging findings (13). The patients who were 18 years old or older, and without an advanced cardiovascular, malignant, metabolic or liver disease, hematological pathology, acquired immunodeficiency syndrome, and not pregnant were included in the study. Patients, who were younger than 18, with advanced cardiovascular, metabolic, liver, chronic inflammatory diseases, cancer, or acquired immunodeficiency syndrome, or pregnant, were excluded from the study.

Statistical analysis

The study data were analyzed with SPSS 21.0 (IBM Corporation, Armonk, NY, USA) software. Kolmogorov-Smirnov and Shapiro-Wilk normality tests were conducted to determine the normal distribution of continuous variables. Parametric numerical data were presented in means ± standard deviations, and qualitative data were presented in percentages. Student's t-test was employed to compare the independent groups. Chi-Square test (cross-tab) was used to compare categorical variables between the groups. Receiver operating characteristic (ROC) curve analysis was conducted on the CRP, NAR, PLR, NLR, SII and SIRI findings between

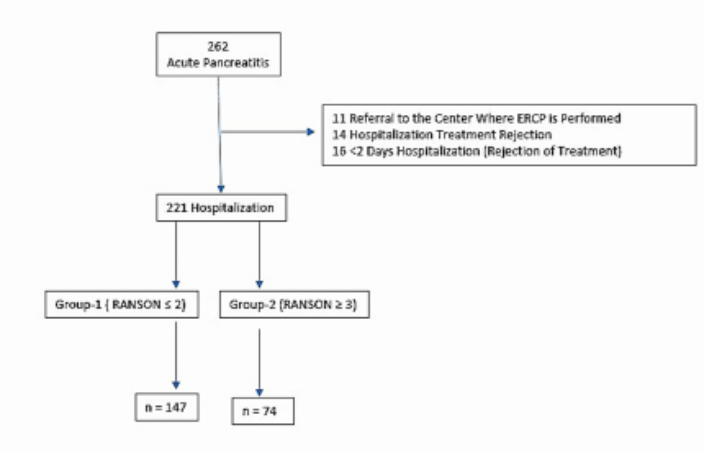

Figure 1. Study patient flow chart

the groups. ROC curve analysis results were presented as % specificity, % sensitivity (area under the ROC curve [AUC], p, 95% confidence interval [CI]). P < 0.005 was accepted as statistically significant in all analyses.

RESULTS

There was no significant difference in gender distribution between Group 1 (n=147, female (F)/male (M)=78/69) and Group 2 (n=74, F/M=48/26) participants (n=221) (p=0.094). However, the mean age was significantly different between the groups, with Group 1 having a mean age of 53.3±17.9 years and Group 2 having a mean age of 74.5±11.9 years (p<0.001). Laboratory parameters showed notable differences between the groups. In Group 2, CRP (p=0.001), NAR (p<0.001), PLR (p<0.001), NLR (p<0.001), SII (p<0.001), SIRI (p<0.001), and the hospitalization period (p<0.001) were significantly higher compared to Group 1 (Table 1). Additionally, Group 2 had significantly higher glucose (p<0.001), creatinine (p<0.001), AST (p=0.004), total bilirubin (p=0.001), direct bilirubin (p=0.001), LDH (p<0.001), white blood cell count (p<0.001), and neutrophil count (p<0.001), whereas the lymphocyte count was significantly lower (p<0.001) (Table 1).

ROC analysis was performed to evaluate the diagnostic value of CRP, NAR, PLR, NLR, SII, and SIRI in distinguishing Group 1 and Group 2 patients. The analysis demonstrated that the specificity of CRP was 54.10%, NAR was 89.80%, PLR was 72.79%, NLR was 57.82%, SII was 68.71%, and SIRI was 76.19% (Table 2). Among these markers, NAR showed the highest specificity (89.80%), while SIRI had a specificity of 76.19%, indicating their potential utility in distinguishing between the patient groups. Additionally, NLR demonstrated the highest sensitivity (79.73%), followed by SII (63.51%) and CRP (66.67%). These findings suggest that systemic immune-inflammatory indices, particularly NLR, SII, and SIRI, may serve as useful indicators for differentiating between the groups.

Table 1: Patient and control demographics and laboratory data

	Group 1	Group 2	p
N (F/M)	147(78/69)	74(48/26)	0.094
Age	53.36 ±17.93	74.55 ±11.91	<0.001
Glucose (mg/dL)	131.74±46.41	168.83±71.17	<0.001
Creatinine (mg/dL)	0.92±1.06	1.64±1.85	<0.001
Albumin (g/L)	38.43±4.57	38.77±21.40	0.856
AST (U/L)	160.82±211	271.45±355.43	0.004
ALT (U/L)	154.55±198.83	169.60±179.19	0.584
Total Bilirubin (mg/dL)	1.27±1.36	2.12±2.39	0.001
Direct Bilirubin (mg/dL)	0.57±0.87	1.07±1.42	0.001
Amylase (U/L)	1650.93±2499.1	1515.68±1436.28	0.667
Lipase (U/L)	4168.57±6228.13	3050.63±3577.06	0.154
LDH (U/L)	330.13±220.13	692.32±1020.70	<0.001
C-reactive protein (mg/dL)	45.61±55.13	83.51±101.49	0.001
White blood cell (103/mm3)	10.95±3.40	12.99±5.17	<0.001
Lymphocyte (10e3/µL)	1.76±1.06	1.10±0.72	<0.001
Neutrophil (10e3/µL)	8.19±3.34	10.78±5.05	<0.001
Monocytes (10e3/µL)	0.83±1.02	0.96±1.13	0.367
Hemoglobin (mg/dL)	15.21±18.11	12.6±2.23	0.218
Platelet (10^3/mm3)	266.93±85	242.90±88.29	0.052
NAR	0.2158±0.09265	0.3166±0.18095	<0.001
PLR	210.554±160.2084	369.7904±457.99764	<0.001
NLR	7.1494±6.74104	15.440±14.68	<0.001
SII	1894.97±2015.82	3908.43±4325.60	<0.001
SIRI	5.14±4.98	15.93±26.18	<0.001
Hospitalization period	6.24±4.74	12.32±13.75	<0.001

N (F/M): Number of patients (Female/Male), AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate Dehydrogenase, NLR: Neutrophil / Lymphocyte Ratio, NAR: Neutrophil / Albumin Ratio, PLR: Platelet to leukocyte ratio, SII: Systemic Immune Inflammation, SIRI: Systemic Inflammation Response Index, p < 0.005 was accepted as statistically significant in all analyses.

Furthermore, the significantly prolonged hospitalization period in Group 2 suggests a potential association between these inflammatory markers and disease severity (Table 2).

DISCUSSION

It was determined that CRP (p = 0.001), NAR (p<0.001), PLR (p<0.001), NLR (p<0.001), SII (p<0.001), SIRI (p<0.001) and length of hospitalization were significantly higher in Group 2 (p<0.001).

AP is an inflammatory disease that can progress from local abdominal pain to mortality. Various scoring systems aim to determine disease severity and prognosis (14,15). The most frequently used system is the Ranson criteria. The limitation of the Ranson criteria is that its measurements become significant only after 48 hours (16,17). Thus, studies on several scoring systems or biomarkers that aim to predict mortality and disease severity at the time of the admission have been increasing. The most frequently used biomarkers are the inflammatory biomarkers.

Several studies have been conducted on CRP, the most commonly used inflammation indicator, in AP. Although it was demonstrated that CRP levels and disease severity were associated with the prognosis of AP and could guide the treatment, Rau et al. compared procalcitonin and CRP values and reported that procalcitonin was more valuable as a marker of early diagnosis and prognosis (18,19). Similar to previous findings, our study demonstrated that the CRP level increases with disease severity and is a significant parameter. However, it can be suggested that the lack of significant findings in a comparative ROC study conducted with other inflammatory parameters revealed two significant consequences for us. The first one is the fact that CRP could not be demonstrated to be specific or sensitive to any inflammatory event. The second one is to serve as an additional indicator for the transparency of the findings in this study.

Table 2: Receiver operating characteristic analyses on CRP, NAR, PLR, NLR, SII, and SIRI in the Groups 1 and 2

	Cut Off (ng/mL)	AUC	95% CI	Sensitivity	Specificity	PPD	NPD	p
CRP	>19.8	0.615	0.541 - 0.685	66.67	54.10	44.0	75.0	0.0080
NAR	>0.32	0.682	0.616 - 0.743	41.89	89.80	67.4	75.4	<0.001
PLR	>245.74	0.659	0.592 - 0.721	55.41	72.79	50.6	76.4	<0.001
NLR	>5.70	0.734	0.670 - 0.791	79.73	57.82	48.8	85.0	<0.001
SII	>2024	0.687	0.621 - 0.747	63.51	68.71	50.5	78.9	<0.001
SIRI	>7	0.694	0.629 - 0.754	55.41	76.19	53.9	77.2	<0.001

Abbreviations: CRP: C-reactive protein, NLR: Neutrophil/Lymphocyte Ratio, NAR: Neutrophil/Albumin Ratio, PLR: Platelet to leukocyte ratio, SII: Systemic Immune Inflammation, SIRI: Systemic Inflammation Response Index, AUC: Area Under the Curve, PPD: Positive Predictive Value, NPD: Negative Predictive Value, p < 0.005 was accepted as statistically significant in all analyses.

Hematological inflammatory parameters or indices have been studied in inflammatory diseases since they are fast, available in several centers, and could be calculated easily. Whereas NLR and PLR have been the most commonly used hematological inflammatory parameters, NAR, SII, and SIRI inflammatory indices have just been investigated recently.

Neutrophils are precursor cells of the immune system defense, and it was reported that they are responsible for the synthesis of cytokine, chemokine, and growth factor, in addition to the production of antimicrobial agents (20). They stimulate cytokine secretion in platelets, much like neutrophils, during the early stages of inflammation. High cytokine levels have been reported to play a crucial role in linking inflammation to microvascular dysfunction by promoting the production of new neutrophils and platelets (21,22). Several studies demonstrated that NLR levels were high in pancreatitis. Suppiah A. et al. reported that elevation in NLR during the first 48 hours of admission was significantly associated with severe AP and an independent negative prognostic indicator of AP (23). Similarly, PLR was demonstrated to increase in inflammatory events and AP. Consistent with the literature, it was elevated in severe AP in the present study. This significant difference between the Groups 1 and 2 was quite interesting. The Ranson criteria scores were higher in the Group 2, and although this finding was due to the severity of AP, the mean age was higher in the Group 2 when compared to the Group 1. Since the immune response occurs later in the elderly, this significant difference is likely associated with the severity of pancreatitis.

NAR is an effective biomarker calculated with neutrophil and albumin counts, providing a cost-effective and easily accessible indicator of systemic inflammation. Previous studies have shown that NAR can predict conditions such as acute kidney injury, cardiogenic shock, myocardial infarction, and cancer (7,24,25). However, there are only a few studies in the literature examining the relationship between NAR and disease severity in other inflammatory conditions, including pancreatitis. The prognostic significance of NAR in severe inflammation has been widely discussed in recent years (6,26). In our study, we found that NAR was significantly higher in Group 2 compared to Group 1 ($p<0.001$), suggesting its potential role as an indicator of disease severity. Moreover, ROC analysis demonstrated that NAR had the highest specificity (89.80%) among all inflammatory markers, emphasizing its predictive value. These findings are consistent with previous reports highlighting the role of NAR as a prognostic biomarker. The ability of NAR to distinguish between different patient groups with high specificity suggests that it may be a valuable tool in clinical decision-making, particularly in identifying patients with a more severe disease course. Furthermore, considering the easy accessibility and low cost of NAR measurement, its integration into routine clinical practice could enhance early risk stratification and management strategies. These findings reinforce the importance of systemic immune-inflammatory markers and suggest that NAR may serve as a clinically useful parameter in assessing disease severity.

Apart from CRP and the proportional parameters (NLR, PLR), the systemic immune inflammation index (SII) that includes a combination of neutrophil, lymphocyte, and platelet counts, and SIRI, formulated based on neutrophils, lymphocytes, and monocytes, were initially used by Hu et al. in 2014 to analyze the prognosis of hepatocellular carcinoma (27). In recent years, SII has been used as an indicator to predict and evaluate neurological and inflammatory diseases, and carcinomas (28-30). The prognostic value of SII was evaluated in a study conducted with 103 pediatric blunt abdominal trauma patients and it was found that higher SII scores were associated with increased mortality. The study reported that an SII intercept of 890.47×10^3/L had 95.7% sensitivity and 62.5% specificity in predicting mortality in these patients (31). In particular, high SII levels have been shown to be associated with disease severity in patients with AP. In another study conducted with 101 AP patients, patients with severe AP were found to have significantly higher SII values compared to patients with mild acute pancreatitis. The study revealed that SII could be an early indicator in distinguishing severe AP from mild AP with 92.9% sensitivity and 87.7% specificity (32). Yasak et al. reported that SII was significantly elevated with the increase in AP severity, and the sensitivity of SII was 72.73% and its specificity was 58.21% in the differentiation of severe AP (33). In another study, AP with higher SII was found more likely to be severe (sensitivity = 92.9%, specificity = 87.7%). The predictive power of SII for the severity of AP was more specific when compared to PLR (sensitivity = 82.1%, specificity = 84.9%) and NLR (sensitivity = 82.1%, specificity = 82.2%) (32). In the present study, it was determined that SII was more specific and sensitive compared to PLR, and it was more specific compared to NLR but demonstrated lower sensitivity. In a study conducted by Silva-Vaz et al., SIRI was employed for the first time as a new prognostic tool for AP severity (34). Similarly, in our study, it was observed that the SII could serve as a useful biomarker for assessing the severity of AP. When compared to PLR and NLR, SII demonstrated higher specificity, enabling a more reliable differentiation of AP severity. Additionally, while the prognostic value of SIRI has been previously established, our study found that SII exhibited a stronger predictive capacity for AP severity than SIRI. Our findings highlight the potential role of SII in clinical practice as a valuable tool for the rapid and accurate determination of AP severity.

Limitations of the study

The present retrospective study was conducted with a small sample size in a single center. Furthermore, the study is cross-sectional, preventing clear findings on causality. Due to the limitations of the current study findings, further studies should be conducted with larger samples in several centers to confirm these findings.

CONCLUSION

To prevent mortality and morbidity in AP patients induced by a chain of inflammatory events, early diagnosis, rapid treatment, and prediction of severe acute pancreatitis are significant in follow-up and prognosis. The inflammatory markers NLR, NAR, PLR, SII, and SIRI are easily accessible and rapid parameters that could be employed to predict AP severity. Among these parameters, NAR is more specific in whereas NLR is more sensitive in AP when compared to others.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: For the study, ethical permission was received from the Fırat University Non-Interventional Research Ethics Committee, dated March 05, 2024, numbered 2024/04-16 and the rules of the Declaration of Helsinki were followed to carry out this study.

Athorship Contributions: Concept: MFU, MY, Design: MFU, MY, Supervising: MFU, MT, EST, Financing and equipment: MFU, MT, EST, Data collection and entry: MFU, EST, MT Analysis and interpretation: MFU, MY, Literature search: MFU, MT, EST Writing: MFU, MT, Critical review: MFU, EST, MT

REFERENCES

1. Ruiz-Rebollo ML, Muñoz-Moreno MF, Mayo-Iscar A, Udaondo-Cascante MA, Nistal RB. Statin intake can decrease acute pancreatitis severit. Pancreatology. 2019;19(6):807-812. doi: 10.1016/j.pan.2019.07.004.

2. James TW, Crockett SD. Management of acute pancreatitis in the first 72 hours. Curr Opin Gastroenterol. 2018;34(5):330-335. doi: 10.1097/MOG.0000000000000456.

3. Li Y, Zhao Y, Feng L, Guo R. Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. BMJ Open. 2017;7(3):e013206. doi: 10.1136/bmjopen-2016-013206.

4. Asghar MS, Khan NA, Haider Kazmi SJ, Ahmed A, Hassan M, Jawed R, et al. Hematological parameters predicting severity and mortality in COVID-19 patients of Pakistan: a retrospective comparative analysis. J Community Hosp Intern Med Perspect. 2020;10(6):514-520. doi: 10.1080/20009666.2020.1816276.

5. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6-e12. doi: 10.1016/j.jinf.2020.04.002.

6. Tingle SJ, Severs GR, Goodfellow M, Moir JA, White SA. NARCA: A novel prognostic scoring system using neutrophil-albumin ratio and Ca19-9 to predict overall survival in palliative pancreatic cancer. J Surg Oncol. 2018;118(4):680-686. doi: 10.1002/jso.25209.

7. Wang B, Li D, Cheng B, Ying B, Gong Y. The Neutrophil Percentage-to-Albumin Ratio Is Associated with All-Cause Mortality in Critically ill Patients with Acute Kidney Injury. Biomed Res Int. 2020;2020:5687672. doi: 10.1155/2020/5687672.

8. Gong Y, Li D, Cheng B, Ying B, Wang B. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. Epidemiol Infect. 2020;148:e87. doi: 10.1017/S0950268820000771.

9. Xie R, Xiao M, Li L, Ma N, Liu M, Huang X, et al. Association between SII and hepatic steatosis and liver fibrosis: A population-based study. Front Immunol. 2022;13:925690. doi: 10.3389/fimmu.2022.925690.

10. Geng Y, Zhu D, Wu C, Wu J, Wang Q, Li R, et al. A novel systemic inflammation response index (SIRI) for predicting postoperative survival of patients with esophageal squamous cell carcinoma. Int Immunopharmacol. 2018;65:503-510. doi: 10.1016/j.intimp.2018.10.002.

11. Balas Ş, Çınkıl CN, Apaydın M. Şiddetli pankreatiti öngörmede yeni biyobelirteç; Sistemik immün-inflamasyon indeksi. Turk J Clin Lab. 2023; 3: 464-469. doi: 10.18663/tjcl.1333413

12. Altuğ E, Çakir A, Kilavuz H, Şener K, Eyüpoğlu G, Güven R. Diagnostic Value of Systemic Immuneinflammation Index in Patients with Acute Pancreatitis. Southern Clinics of Istanbul Eurasia. 2023;34(2). doi: 10.14744/scie.2023.70893.

13. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012:

revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-111. doi: 10.1136/gutjnl-2012-302779.

14. Zeytunlu M, Akyıldız M, Tekeşin O, Ersöz G, Özütemiz Ö, Çoker A, et al. Akut pankreatit olgularının kanıta dayalı tıp kılavuzları rehberliğinde incelenmesi. Akademik Gastroenteroloji Dergisi 2005;4:146-53.
15. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990;174(2):331-336. doi: 10.1148/radiology.174.2.2296641.
16. Jense EH, Borja D, Al-Refaıe WB, Vickers SM. Exocrine Pancreas. In: Sabiston DC, editor. Sabiston Textbook of Surgery. 19th ed. Philadelphia: W.B. Saunders; 2012; p:1515-1547.
17. Brunicardi FC, Anderson DK, Biliar TR, Dunn DL, Hunter JG, Pollock RE. Pankreas. In: Fisher EW, Andersen DK, Bell RH, Saluja AK, Brunicardi FC, editors. Schwartz's Princıples of Surgery. Schwartz Cerrahinin İlkeleri. 8. Baskı, Çeviren: Geçim İE, Demirkan A, Tarlan Yayıncılık, Ankara. 2008;s:1265-1340.
18. Rau BM, Kemppainen EA, Gumbs AA, Büchler MW, Wegscheider K, Bassi C, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenter study. Ann Surg. 2007;245(5):745-754. doi: 10.1097/01.sla.0000252443.22360.46.
19. Pepys MB, Hirschfield GM. C-reactive protein: a critical update [published correction appears in J Clin Invest. 2003;112(2):299]. J Clin Invest. 2003;111(12):1805-1812.
20. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011;11(8):519-531. doi: 10.1038/nri3024.
21. Cho SK, Jung S, Lee KJ, Kim JW. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio can predict the severity of gallstone pancreatitis. BMC Gastroenterol. 2018;18(1):18. doi: 10.1186/s12876-018-0748-4.
22. Stokes KY, Granger DN. Platelets: a critical link between inflammation and microvascular dysfunction. J Physiol. 2012;590(5):1023-1034. doi: 10.1113/jphysiol.2011.225417.
23. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM, et al. The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acute pancreatitis: identification of an optimal NLR. J Gastrointest Surg. 2013;17(4):675-681. doi: 10.1007/s11605-012-2121-1.
24. Sun T, Shen H, Guo Q, Yang J, Zhai G, Zhang J, et al. Association between Neutrophil Percentage-to-Albumin Ratio and All-Cause Mortality in Critically Ill Patients with Coronary Artery Disease. Biomed Res Int. 2020;2020:8137576. doi: 10.1155/2020/8137576
25. Ferro M, Babă DF, de Cobelli O, Musi G, Lucarelli G, Terracciano D, et al. Neutrophil percentage-to-albumin ratio predicts mortality in bladder cancer patients treated with neoadjuvant chemotherapy followed by radical cystectomy. Future Sci OA. 2021;7(7):FSO709. doi: 10.2144/fsoa-2021-0008.
26. Tawfik B, Mokdad AA, Patel PM, Li HC, Huerta S. The neutrophil to albumin ratio as a predictor of pathological complete response in rectal cancer patients following neoadjuvant chemoradiation. Anticancer Drugs. 2016;27(9):879-883. doi: 10.1097/CAD.0000000000000411.
27. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-6222. doi: 10.1158/1078-0432.CCR-14-0442.
28. Dionisie V, Filip GA, Manea MC, Movileanu RC, Moisa E, Manea M, et al. Neutrophil-to-Lymphocyte Ratio, a Novel Inflammatory Marker, as a Predictor of Bipolar Type in Depressed Patients: A Quest for Biological Markers. J Clin Med. 2021;10(9):1924. doi: 10.3390/jcm10091924.
29. Bartl T, Bekos C, Postl M, Alexander R, Polterauer S, Stefanie A, et al. The systemic immune-inflammation index (SII) is an independent prognostic parameter of survival in patients with invasive vulvar cancer. J Gynecol Oncol. 2021;32(1):e1. doi: 10.3802/jgo.2021.32.e1.
30. Erdogan T. Role of systemic immune-inflammation index in asthma and NSAID-exacerbated respiratory disease. Clin Respir J. 2021;15(4):400-405. doi: 10.1111/crj.13314.
31. Altuğ E, Altundağ İ, Çakır A, Şener K, Korkut S, Güven R. Prognostic Value of Systemic Immune-inflammation Index in Patients with Pediatric Blunt Abdominal Trauma. Glob Emerg Crit Care. 2024 Aug;3(2):87-92. doi:10.4274/globecc.galenos.2024.30074.
32. Liu X, Guan G, Cui X, Liu Y, Liu Y, Luo F. Systemic Immune-Inflammation Index (SII) Can Be an Early Indicator for Predicting the Severity of Acute Pancreatitis: A Retrospective Study. Int J Gen Med. 2021;14:9483-9489. Published 2021 Dec 8. doi:10.2147/IJGM.S343110.

33. Yasak İ.H ve Yılmaz M. The relationship between systemic immune inflammation index and length of hospitalization in acute pancreatitis. AAnn Clin Anal Med 2023;14(4):340-344.

34. Silva-Vaz P, Jarak I, Rato L, Oliveira PF, Morgado-Nunes S, Paulino A, et al. Plasmatic Oxidative and Metabonomic Profile of Patients with Different Degrees of Biliary Acute Pancreatitis Severity. Antioxidants (Basel). 2021;10(6):988. doi: 10.3390/antiox10060988.

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1575878
Interdiscip Med J 2025;16(54):45-49

Effect of COVID-19 mRNA vaccination on prostate specific antigen levels in prostate cancer patients

Ali Borekoglu[1], Barıs Saylam[1], Nebil Akdogan[2], Tunahan Ates[3], Ali Inal[4], Fatih Gokalp[5]

[1]Mersin City Training and Research Hospital, Department of Urology, Mersin, Türkiye
[2]Cukurova University Faculty of Medicine, Department of Urology, Adana, Türkiye
[3]Defne State Hospital, Department of Urology, Hatay, Türkiye
[4]Mersin City Training and Research Hospital, Department of Medical Oncology, Mersin, Türkiye
[5]Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Urology, Hatay, Türkiye

Abstract

Objective: The effect of COVID-19 mRNA vaccines on prostate specific antigen (PSA) levels in prostate cancer patients remains unclear. In this study, we aimed to evaluate the effects of COVID-19 mRNA vaccination on PSA levels in patients with prostate cancer.

Method: Retrospective data were collected from patients diagnosed with prostate cancer (ICD-10 code C61). Inclusion criteria encompassed patients with pre-vaccination PSA levels of ≤2 ng/mL, no metastases, no active urinary tract infection and no history of urinary catheterization.

Results: Of the 333 patients initially screened, 176 were excluded due to missing data. Sixty-eight patients with PSA level > 2 ng/mL and 10 patients who developed urinary tract infection during follow-up were also excluded. The study included 89 patients (mean age: 70.77±5.88 years). Fifteen of these patients were between the ages of 55-65 years and the remaining 64 patients were between the ages of 65-83 years. There was no significant difference in PSA measurements between the first, second, and third doses of COVID-19 mRNA vaccine.

Conclusion: Invaluable information about the effect of COVID-19 mRNA vaccination on PSA levels in prostate cancer patients was provided. The findings suggest that COVID-19 mRNA vaccination has no significant effect on PSA levels in prostate cancer patients admitted to our urology and oncology clinics. However, further studies with larger sample size and longer follow-up period are needed to confirm these findings and better understand the relationship between COVID-19 vaccination and PSA levels in prostate cancer patients.

Keywords: COVID-19, mRNA vaccines, severe acute respiratory syndrome coronavirus 2, prostate cancer, prostate specific antigen, pandemic

INTRODUCTION

Coronavirus disease (COVID-19) unexpectedly entered our lives in December 2019 and has affected millions. In the early stages of the pandemic, SARS-CoV-2 was thought to target only the respiratory system. However, recent studies have shown that the virus can target all tissues expressing angiotensin-converting enzyme 2 (ACE-2), which is responsible for attachment to host cells. Furthermore, studies have shown that SARS-CoV-2 invades and spreads into host cells using the transmembrane protease serine 2 (TMPRSS2) in addition to the ACE-2 protein (1). After binding to the ACE-2 receptor, SARS-CoV-2 is separated from the spike protein by the TMPRSS2 enzyme, and binds to the cell membrane to enter the cell (2). The TMPRSS2 gene is highly expressed in human prostate epithelial cells (3). In addition to the expression of angiotensin-converting enzym-2 (ACE2) receptors and TMPRSS2 enzyme in the human prostate, the regulation of TMPRSS2 by androgens makes prostate tissue a potential target for SARS-CoV-2 infection (2,4). Similarly, COVID-19 has been detected in many body fluids including urine, and it has also been detected in prostate tissue (5,6). In addition, infection with COVID-19 has been associated with a slight increase in prostate specific antigen (PSA) levels in patients with benign prostatic hyperplasia (7).

Cite this article: Borekoglu A, Saylam B, Akdogan N, Ates T, Inal A, Gokalp F. Effect of COVID-19 mRNA vaccination on prostate specific antigen levels in prostate cancer patients. Interdiscip Med J. 2025;16(54):45-49. https://doi.org/10.17944/interdiscip.1575878

Corresponding Author: Dr. Tunahan Ateş, Defne State Hospital, Department of Urology, Hatay, Türkiye
Email: drtunahanates0101@gmail.com
ORCID iD: 0000-0001-9087-290X

Received: Oct 30, 2024
Accepted: Mar 16, 2025

Vaccination is a type of immunotherapy that induces a local inflammatory response in the body. The spike protein has been the target of many vaccines because of the virus's constant ability to infect host cells through interaction with the ACE2 receptor (8). A literature search revealed that no clinical trials have examined the effects of COVID-19 vaccines on PSA levels, and the available studies are limited to case reports (9).

The spike protein has gained attention as a potential target for virus entry into cells and for the development of vaccine-induced immunity. It has been suggested that SARS-CoV-2 infection could affect the prostate and disrupt its structure (7). Therefore, the present study aims to investigate the effects of COVID-19 vaccines produced with the spike protein of SARS-CoV-2 on PSA levels in patients with prostate cancer.

METHOD

After approval by the local ethics committee (ethics committee decision dated 20/04/2022, number 2022/293), the data of patients who were diagnosed with prostate cancer with code C61 (International Statistical Classification of Diseases and Related Health Problems (ICD-10)) and followed up by Health Sciences University, Mersin City Training and Research Hospital (between August 2019 and January 2021) were retrospectively collected. Patients with a pre-vaccination laboratory PSA level (Kit: Immunoassay Program, Ref: 02676506, Siemens ADVIA Centaur XPT) of 2 ng/mL or less and patients with clinically and radiologically proven absence of metastases were included in the study. In addition, patients who had not been diagnosed with COVID-19, had no active infection such as urinary tract infection (UTI), and had no urinary catheter placed were included in the study.

In Türkiye, the use of mRNA vaccines against COVID-19 is recommended by the World Health Organization as the first dose and a booster dose after six months. Patients who had been vaccinated according to this protocol were included in the study. Patients with PSA levels of 2 ng/mL or more during the relevant period were excluded from the study due to the possibility of metastatic disease causing a PSA increase. In addition, patients who underwent radical prostatectomy, diagnosed clinically and/or by laboratory testing UTI, and had a history of urethral trauma or catheterization were excluded from the study because they were associated with a potentially elevated PSA level. Prevaccination and postvaccination PSA were recorded and documented on a standard sheet.

Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Since the data did not follow a normal distribution, non-parametric tests were applied. Quantitative data were presented as mean and standard deviation and qualitative data were presented as frequency and percentage. Comparisons between groups were conducted using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. Analyzes were performed with the Statistical Package for Social Sciences program (SPSS Inc, Chicago, IL) version 20.0. Statistical significance was set at $p<0.05$.

RESULTS

The data of 333 patients were retrospectively screened. Of those, 176 patients whose data could not be accessed fully were excluded from the study. Additionally, 68 patients with a PSA level over 2 ng/mL and 10 patients who developed urinary tract infections during follow-up were excluded. A total of 89 patients were enrolled in this study (Figure 1). The

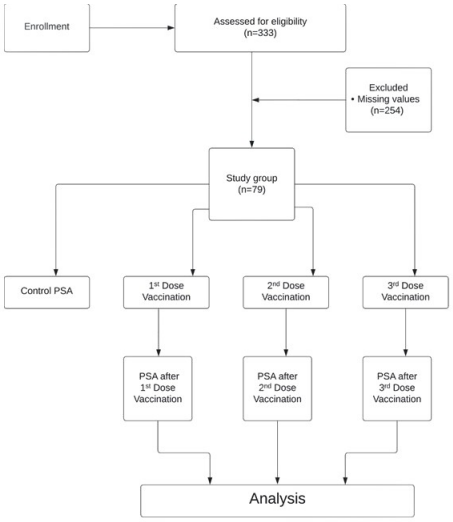

Figure 1. Flow chart of patient selection

mean age was 70.77±5.88 years. A total of 15 patients were between the ages of 55-65 and the remaining 64 were between 65-83 years. In this study, no significant difference was found in PSA measurements between mRNA first, second and third doses of COVID-19 vaccinations ($p>0.05$; Table 1).

DISCUSSION

In this study, it was found that mRNA-based vaccines employed for COVID-19 and the administered number of doses did not have an effect on PSA levels. The importance of early diagnosis of oncological diseases is crucial, and it allows for a higher chance of cure with lower progression to metastatic disease, limited use of aggressive treatments, and improvement in quality of life, as well as a reduction in disease-specific mortality, among other advantages. Screening programs have also great importance for early diagnosis.

Table 1. Prostate specific antigen values of the patients

	Control	1st Measurement	2nd Measurement	3rd Measurement
Mean±Standart deviation	0.189±0.365	0.853±3.324	0.399±1.748	0.116±0.190
		Difference 1	Difference 2	Difference 3
Difference (%)		296.698±1386.88	68.092±210.088	188.395±483.701

Wilcoxon rank sum test was used. Intragroup comparisons of Means; 1st Measurement–Control: p=0.537; 2nd Measurement–Control: p=0.460; 3rd Measurement–Control: p=0.619; 2nd Measurement–1st Measurement: p=0.293; 3rd Measurement–1st Measurement: p=0.307; 3rd Measurement–2nd Measurement: p=0.373. Intragroup comparisons of Differences of means in percentage; Difference 1: 1st Measurement–Control; Difference 2: 2nd Measurement – 1st Measurement; Difference 3: 3rd Measurement – 2nd Measurement; Difference 2 – Difference 1: p=0.934; Difference 3–Difference 2: p=0.735.

The PSA is the screening test commonly used worldwide, which was first used in 1981 for monitoring patients with prostate cancer (10). However, the PSA levels do not increase only in malignant diseases, various benign conditions may cause raised levels leading to questions about the specificity of PSA. Therefore, serum PSA level entered clinical practice as a tumor marker to confirm diagnosis and monitor treatment effectiveness, rather than a screening tool in 1987 (11). Although there are rules regarding the limitation of PSA in community screening due to health policies implemented in many countries today, PSA is still used in treating and following patients diagnosed with prostate cancer (12). First reported in December 2019, COVID-19 devastated populations, social structures, and economic growth worldwide, by evolving into a pandemic. Subsequent studies on the disease were accelerated, and it was determined that the agent responsible for this impact was an RNA virus, known as SARS-CoV-2, containing a spike protein that enters the cell using the ACE-2 protein and transmembrane protease serine 2 (TMPRSS2) (13). During the early stages of the pandemic, it was thought that the virus only affected the lungs, in contrast, studies have shown that SARS-CoV-2 can infect all cells expressing ACE-2 protein and TMPRSS2 (1). The prostate gland, similar to the lungs, heart, kidneys, and liver, is an organ with a significant expression of ACE2 receptors. Furthermore, the TMPRSS2 gene is prominently expressed in prostate epithelial cells, making the prostate gland an evident target for SARS-CoV-2. Indeed, recent studies have demonstrated an increase in PSA levels during the active period of COVID-19, and the presence of the COVID-19 genome in prostate tissue supports the idea of prostatic involvement of SARS-CoV-2 (6, 7).

There is evidence to suggest that the overall effect of prostatic involvement of SARS-CoV-2 is likely due to an inflammatory process caused by cytokine release, systemic procoagulant and disseminated intravascular coagulation (DIC), structural damage, local vascular permeability increase, and tissue damage. This is likely due to the mechanism behind the PSA elevation during the acute phase of the infection.

Vaccine applications can sometimes lead to a local inflammatory response in the injection site and its surroundings, and occasionally a systemic response such as hypermetabolic lymph nodes distant from the injection site (9). These responses may sometimes cause dilemmas in the follow-up and management of oncological patients. In particular, in the case of prostate cancer, PSA elevation may be related to disease recurrence, hence it may require additional treatment. In this respect, it is essential to distinguish the cause of the elevation of PSA levels. The knowledge of vaccination might be an evident factor to contribute to the management of patients with prostate cancer. It is estimated that the present study will shed light on the management of these patients. In a recent study, it was shown that exposing human prostate cancer cell lines (LNCaP) to the isolated spike protein of SARS-CoV-2 in vitro resulted in a decrease in cell survival. Authors suggested that the SARS-CoV-2 spike protein has a significant negative effect on the proliferation of LNCaP cells, and in vitro experiments have shown that the spike protein reduces cell proliferation and induces apoptosis through a two-pronged approach, leading to a decreased survival of prostate cancer cells. Researchers also suggested that COVID-19 vaccination could potentially provide additional benefits in the management of prostate cancer (14). Nucleic acid vaccines, such as mRNA vaccines, mimic natural infection by inducing endogenous antigen production and generating strong T and B cell responses, although they are not completely infectious (15). The mRNA vaccine used for COVID-19 also contains the mRNA sequence of the spike protein. After the vaccine reaches the body, millions of copies of the sSpike protein are produced within cells through this mRNA sequence. This stimulates the body to create antibodies against the cells producing the protein (8, 16).

The findings of this study suggest that mRNA vaccines do not significantly impact PSA levels in prostate cancer patients, providing reassurance for clinicians regarding their safety and use in this population. These results are particularly important for alleviating concerns about potential vaccine-related fluctuations in PSA, which could otherwise lead to unnecessary clinical interventions or misinterpretations of disease progression. However, despite the overall stability

of PSA levels observed in our study, individualized PSA monitoring remains essential. Certain patient subgroups, such as those with advanced disease, those undergoing androgen deprivation therapy, or individuals with unique immunological responses, may exhibit variations that were not captured in our study. Additionally, potential transient fluctuations in PSA following vaccination, even if not clinically significant on a broader scale, warrant further investigation to ensure optimal patient management. Given these considerations, further research is needed to explore potential subgroup differences and to provide more comprehensive clinical guidance. Such investigations will contribute to more personalized prostate cancer monitoring strategies and ensure that vaccination remains a safe and effective preventive measure in this patient population.

Limitations of the study

The absence of PSA elevation or reduction observed in the present study after administering mRNA vaccines produced using spike protein may be attributed to the fact that the vaccine was developed in an in vitro environment, and the results may be influenced by the complex inflammatory response that can sometimes have a widespread effect on the body.

As can be seen, our study was performed retrospectively. This situation brings along some limitations. Although no significant overall changes in PSA levels were observed, individual variations were not specifically analyzed. This represents a limitation, as some patients may exhibit different biological responses to mRNA vaccination. Future studies should focus on assessing PSA level fluctuations at an individual level to better understand potential variations and their clinical implications. Since our study was single-center, the number of patients was not relatively high. Studies with a larger number of patients are needed. Future studies should focus on multicenter studies with larger cohorts to validate these results and provide more comprehensive insights into the potential effects of mRNA vaccines on PSA levels in prostate cancer patients.

CONCLUSION

It can be suggested that mRNA vaccines showed no interaction with PSA levels which might cause confusion in the management of patients with prostate cancer. The present study is the first research in the literature to evaluate the effect of mRNA-based vaccines on PSA levels. Further studies with larger sample sizes and development in mRNA technologies might trigger new treatment modalities in which the spike protein can be used to treat prostate cancer cells.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: Ethical permission was obtained from the Mersin University, Human Research Ethics Committee for this study with date 20/04/2024 and number 293, and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions: Concept: TA, NA, Design: AB, NA, FG, Supervising: AI, AB, Financing and equipment: AB, BS, AI, FG Data collection and entry: NA, BS, Analysis and interpretation: AI, TA, FG, Literature search: AB, BS, Writing: AB, AI, Critical review: BS, AI.

Thanks: The authors would like to thank the staff of the Oncology Department of Mersin City Hospital.

REFERENCES

1. Beyerstedt S, Casaro EB, Rangel EB, Covid -19 angiotensin converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis 2021; 40:905-919. doi:10.1007/s10096-020-04138-6
2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS CoV-2 Cell entry depends on ACE2 and TMPRSS2 and blocked by a clinically proven protease inhibitor. Cell.2020;181:271-280. doi:10.1016/j.cell.2020.02.052
3. Mauvais-Jarvis F. Do anti androgeneshave potential as therapeutics for COVİD – 19? Endocrinology.2021;162(8);bqab114. doi:10.1210/endocr/bqab114
4. Djomkam ALZ, Olwal CO, Sala TB, Paemka L. Commentary: SARS CoV -2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Front Oncol.2020;10:1448. doi:10.3389/fonc.2020.01448
5. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA.2020;323(18):1843-1844. doi:10.1001/jama.2020.3786
6. Elsaqa M, Rao A, Liu L, Hua Y, Volz M, Morris R, Risinger J, Tayeb MME. Molecular detection of the COVID-19 genome in prostatic tissue of patients with previous infection. Proc (Bayl Univ Med Cent). 2022 Jul 19;35(6):759-761. doi: 10.1080/08998280.2022.2101178.
7. Cinislioglu AE, Demirdogen SO, Cinislioglu N, et al. Variation of serum PSA levels in COVİD-19 infected

male patients with benign prostatic hyperplasia (BPH): a prospective cohort study. Urology.2022;159:16-21. doi:10.1016/j.urology.2021.09.016

8. Han HJ, Nwagwu C, Anyim O, Ekweremadu, Kim S. Covid-19 and cancer: from basic mechanisms to vaccine development using nanotechnology. IntImmunopharmacol.2021;90:107247. doi:10.1016/j.intimp.2020.107247
9. Andresciani F, Ricci M, Grasso RF, Zobel BB, Quattrocchi CC. COVID-19 vaccination simulating lymph node progression in a patient with prostate cancer. Radiol Case Rep. 2022 Jun 17;17(9):2996-2999. doi: 10.1016/j.radcr.2022.05.072.
10. Kuriyama, M. et al. Use of human prostate-specific antigen in monitoring prostate cancer. Cancer Res.41, 3874–3876 (1981)
11. Stamey, T. A. et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N. Engl. J. Med. 317, 909–916 (1987). doi:10.1056/NEJM198710083171501
12. Van Poppel, H., Albreht, T., Basu, P. et al. Serum PSA-based early detection of prostate cancer in Europe and globally: past, present and future. Nat Rev Urol; 19:562–572 (2022). https://doi.org/10.1038/s41585-022-00638-6
13. Umakanthan S, Sahu P, Ranada AV, Bukelo MM, Rao JS, Abrahao-Machado LF et al. Rigin transmission, diagnosis and management of coronavirus disease 2019 (COVİD-19) Postgrad Med J.2020;96(1142):753-8. doi:10.1136/postgradmedj-2020-138234
14. Johnson BD, Zhu Z, Lequio M, Powers CGD, Bai Q, Xiao H, Fajardo E, Wakefield MR, Fang Y. SARS-CoV-2 spike protein inhibits growth of prostate cancer: a potential role of the COVID-19 vaccine killing two birds with one stone. Med Oncol. 2022 Jan 20;39(3):32. doi: 10.1007/s12032-021-01628-1.
15. Hwang JK, Zhang T, Wang AZ, Li Z. COVID-19 vaccines for patients with cancer: benefits likely outweigh risks. J Hematol Oncol. 2021 Feb 27;14(1):38. doi: 10.1186/s13045-021-01046-w.
16. Trougakos IP, Terpos E, Alexopoulos H, Politou M, Paraskevis D, Scorilas A, Kastritis E, Andreakos E, Dimopoulos MA. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. Trends Mol Med. 2022 Jul;28(7):542-554. doi: 10.1016/j.molmed.2022.04.007. Epub 2022 Apr 21.

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1573618
Interdiscip Med J 2025;16(54):50-55

The effect of total knee arthroplasty surgery on mean platelet volume, platelet count, and mean platelet volume/platelet count ratio

Esma Karaarslan[1], Yasin Tire[1], Aydın Mermer[1], Nuran Akıncı Ekinci[1], Muhammed Halit Satıcı[1], Betül Kozanhan[1], Ahmet Yıldırım[2]

[1]Konya City Hospital, Department of Anesthesiology and Reanimation, Konya, Türkiye
[2]Konya City Hospital, Department of Orthopedics and Traumatology, Konya, Türkiye

Abstract

Objective: This study aims to investigate the effects of total knee arthroplasty (TKA) surgery on mean platelet volume (MPV), platelet count (Plt), and the MPV/Plt ratio.

Methods: This retrospective study examined the data of 379 patients who underwent total knee arthroplasty at Konya City Hospital between January 1, 2023, and January 1, 2024. Preoperative and postoperative blood tests were analyzed at 12-24 hours (postop1) and 24-48 hours (postop2) intervals. MPV, Plt, and MPV/Plt ratio were recorded and compared. Repeated measures ANOVA test was used for statistical analysis.

Results: A significant increase in MPV and MPV/Plt ratio and a significant decrease in Plt were observed in the postoperative period ($p<0.001$).

Conclusion: The increase in MPV and the decrease in Plt after total knee arthroplasty may indicate an elevated risk of thromboembolic complications. Routine monitoring of MPV, Plt, and the MPV/Plt ratio could be necessary for the erly detection and management of these complications.

Keywords: Total knee arthroplasty, mean platelet volume, platelet count, mean platelet

INTRODUCTION

In aging societies, the number of elderly patients suffering from degenerative knee joint disease is increasing. This condition can cause pain and a decrease or loss in the ability to walk (1). Total knee arthroplasty (TKA) is a proven and effective treatment for relieving arthritic knee pain. (2, 3). While attempting to achieve pain relief with knee arthroplasty surgery, another goal is to minimize complications.

Orthopedic surgery, particularly total knee and total hip arthroplasty, is considered a significant risk factor for perioperative venous thromboembolism. During surgical intervention, the tendency for blood to coagulate increases. Surgical trauma raises the concentrations of coagulation factors in the plasma while lowering the levels of coagulation inhibitors. Additionally, it enhances platelet activity at the site of vascular injury, triggering the release of cytokines, catecholamines, and serotonin, which induce platelet aggregation and increase the propensity for thrombosis. Surgical stress also suppresses fibrinolytic responses (4-6).

Platelets are small, anucleate cells that are vital in the hemostasis process (7). Abnormalities in platelet count (Plt) are critically important in the diagnosis and management of various clinical conditions. Monitoring Plt, especially after major surgical interventions such as knee prosthesis surgery, is crucial for preventing postoperative complications.

Mean platelet volume (MPV), which indicates the average size of platelets, is an important laboratory marker associated with platelet function and activity. Increased MPV is considered a significant risk factor in thromboembolic diseases (4, 5). Larger platelets are more reactive than normal-sized platelets because they have a higher granule content (6, 8). These larger platelets produce more prothrombotic factors, exhibit greater

Cite this article: Karaarslan E, Tire Y, Mermer A, Akıncı-Ekinci N, Satıcı MH, Kozanhan B, Yıldırım A The effect of total knee arthroplasty surgery on mean platelet volume, platelet count, and mean platelet volume/platelet count ratio. Interdiscip Med J. 2025;16(54):50-55. https://doi.org/10.17944/interdiscip.1573618

Corresponding Author: Dr. Esma Karaarslan, Konya City Hospital, Department of Anesthesiology and Reanimation, Konya, Türkiye
Email: esmaayvaz@gmail.com
ORCID iD: 0000-0002-3459-0243

Received: Oct 25, 2024
Accepted: Mar 22, 2025

aggregation in response to adenosine diphosphate (ADP), collagen, or adrenaline, and secrete more thromboxane A2 (TxA2) (9, 10). An increase in MPV is the initial indicator of platelet activation and rises when platelet production and destruction are enhanced by cytokines such as interleukin-3, interleukin-6, and thrombopoietin (11). The thrombotic potential and the effectiveness of hemostatic, vasomotor, and pro-inflammatory functions of larger platelets are greater than those of smaller platelets (12).

The MPV/Plt ratio is considered an important indicator among hematological parameters. This ratio is particularly used in the evaluation of various clinical conditions such as cardiovascular diseases, inflammatory states, and cancer (9, 13-15). In this context, the MPV/Plt ratio emerges as a valuable biomarker in clinical applications.

In this study, it was aimed to investigate the effects of total knee arthroplasty surgery on MPV, Plt, and the MPV/Plt ratio.

METHOD

Ethics approval and registration

This study was conducted through a retrospective review of patients who underwent TKA in the operating rooms of Konya City Hospital between January 1, 2023, and January 1, 2024. Ethical approval for the study was obtained from the KTO Karatay University Ethics Committee on October 14, 2024 (Decision No: E-41901325-200-95694). The Declaration of Helsinki and relevant ethical principles were followed in the research. Patient data were accessed through the Konya City Hospital Electronic Patient Information Management System (HBYS).

Patient population and inclusion/exclusion criteria

The study included patients aged 18 years and older with an American Society of Anesthesiologists (ASA) physical status classification of 1 to 3, who underwent elective knee replacement surgery. Patients were excluded if they had a history of stroke (SVO) and/or transient ischemic attack (TIA), a history of myocardial infarction (MI), coronary artery disease, hematological disorders, thrombophilic conditions, a history of pulmonary thromboembolism (PTE) and/or deep vein thrombosis (DVT), a history of thromboembolic disease, active infections, or elevated infection markers.

Outcome measures

The primary outcome involved a retrospective review of routine blood tests at three different time points. These tests were conducted during the preoperative preparation phase, between 12-24 hours postoperatively and between 24-48 hours postoperatively. MPV, Plt, and the MPV/Plt ratio were recorded from these blood tests. The values measured before surgery were labeled as preoperative (preop), while the postoperative values were categorized as postoperative 1 (postop1) and postoperative 2 (postop2), respectively. Additionally, patient demographics, including age, gender, and ASA score, were recorded for all participants.

Statistical analysis

The data obtained in this study were analyzed using IBM SPSS Statistics 20.0 (IBM-SPSS Inc., Chicago, IL, USA). A total of 379 patients meeting the inclusion criteria were included in the analysis. Continuous variables were expressed as mean and standard deviation or median (25th-75th percentile) based on their distribution, while categorical variables were expressed as frequency and percentage. The normality of the data distribution was assessed using skewness and kurtosis values within the range of -1.5 to +1.5, histogram shapes, and Q-Q plots. For comparisons between measurements, repeated measures ANOVA was used. A p-value of less than 0.05 was considered statistically significant. Additionally, Bonferroni correction was applied for pairwise comparisons, and a p-value of less than 0.05 was deemed statistically significant.

RESULTS

Patients who underwent TKA between January 1, 2023, and January 1, 2024, were retrospectively reviewed. A total of 379 patients meeting the study criteria were included. The patients' demographic characteristics (age, ASA score, and gender) were evaluated (Table 1).

The recorded values of the patients were presented as mean ± standard deviation. Preoperative values were as follows: MPV 10.389±0.868, Plt 283.6±66.3, and MPV/Plt ratio 0.039±0.01 (Table 2).

Table 1. Patient demographic characteristics

Characteristics		n: 379
Age, (year)		65±8
ASA score, n (%)	1	6 (1.6%)
	2	240 (63.3%)
	3	133 (35.1%)
Gender, n(%)	Man	47 (12.4%)
	Woman	332 (87.6%)
ASA: American Society of Anesthesiologists		
Continuous variables are presented as Mean ± SD, while categorical variables are shown as n.(%).		

Tablo 2. MPV, Plt, and MPV/Plt ratio values

	Preop	Postop1	Postop 2	P
MPV	10.389±0.868	10.587±0.870	10.774±0.868	<0.001
Plt	283.6±66.3	244.3±57.1	214.9±51.8	<0.001
MPV/Plt ratio	0.039±0.01	0.046±0.012	0.053±0.015	<0.001
Continuous variables are presented as Mean±SD. MPV, Mean platelet volume; Plt, platelet count				

Postoperatively, at 12-24 hours, MPV1 was 10.587±0.870, Plt1 was 244.3±57.1, and MPV/Plt1 ratio was 0.046±0.012 (Table 2). At 24-48 hours postoperatively, MPV2 was 10.774±0.868, Plt2 was 214.9±51.8, and MPV/Plt2 ratio was 0.053±0.015 (Table 2).

When comparing the preoperative MPV, Plt, and MPV/Plt ratio with the postoperative values at both time points, a statistically significant difference was observed over time ($p<0.001$) (Table 2). Postop MPV1 and MPV2 values were significantly higher compared to preop MPV values ($p<0.001$ for both comparisons). However, the Plt measured at both postop time points was significantly lower than the preop Plt ($p<0.001$ for both comparisons). Additionally, the MPV/Plt1 and MPV/Plt2 ratios were significantly higher than the preop MPV/Plt ratio ($p<0.001$ for both comparisons).

In the first 48 hours following surgery, there was an increase in MPV and the MPV/Plt ratio ($p<0.001$ for both), while the Plt showed a significant decrease ($p<0.001$) when comparing postop values with preop measurements.

DISCUSSION

As a result of the research, it was found that after TKA surgery, patients' MPV and MPV/Plt values increased significantly, while their Plt decreased significantly.

The risk of complications following TKA increases due to the heightened tendency of blood coagulation during surgery and the surgical trauma enhancing coagulation factors and platelet activity (16). MPV is a parameter of routine blood tests. It is low-cost and provides results quickly (17). Additionally, MPV is a commonly used laboratory marker associated with platelet function and activity (4, 5). Studies have found higher MPV values in patients who experienced stroke (18) and acute MI (19, 20) compared to the control group. Additionally, P. Bath and colleagues demonstrated that MPV is a predictor of stroke in patients with a history of cerebrovascular events, and it can predict stroke risk even in the 3.9-year period preceding the event (21). Increased MPV is associated with higher mortality in cardiovascular diseases and is considered an important risk factor. (6, 8) Cameron HA and colleagues also found that MPV was higher in acute MI patients compared to the control group in their study (19). Similarly, there are various studies indicating a relationship between increased MPV and DVT (22, 23).

Both retrospective and prospective studies have shown that large platelets and high MPV are predictors of thrombotic events in predominantly arterial diseases (4). Additionally, the literature indicates that high MPV is associated with various diseases such as MI (24), cerebrovascular thromboembolism (25), portal vein thrombosis (17) and cancer-related thrombosis (26).

İçli et al. (27) reported that MPV values were significantly higher in DVT patients, whether or not they had pulmonary embolism, and that high MPV in DVT patients was associated with pulmonary embolism. Similarly, Gulcan et al. (28) demonstrated that MPV was significantly higher in DVT patients compared to the control group. Aliosmanoglu et al. (17) showed that MPV levels were significantly higher in patients with unexplained portal vein thrombosis compared to control participants.

In this study, it was found that MPV increased significantly following TKA surgery. High MPV is thought to elevate the risk of thrombotic complications, such as DVT and pulmonary embolism. Therefore, regular monitoring of MPV values in patients after TKA may be important for the early detection and management of potential complications. Furthermore, studies in the literature support an association between elevated MPV values and various thrombotic events. High MPV is recognized as a significant risk factor in cardiovascular diseases, cerebrovascular events, and pulmonary hypertension. These findings align with the results of this study suggest that elevated MPV is an essential marker to consider when assessing thrombotic risks.

It has been reported that the Plt decreases by approximately 30% to 60% after major surgical procedures (29, 30). This decrease has been suggested to be related to increased platelet consumption due to the effects of surgery, as well as hemodilution (31).

Plt was also examined in a study conducted by D'Erasmo and colleagues. In this study, it was found that stroke patients with high mortality had low Plt (32). Similarly, in a study conducted by Jin Soo Han and colleagues, it was shown that a low platelet count can activate the coagulation system (33). In various studies, it has been found that patients who have experienced an acute MI have lower Plt compared to the control group (19, 34, 35).

In this study, a significant decrease was found in Plt following TKA surgery, consistent with findings of existing literature. This result reaffirms the impact of major surgical interventions on the reduction of Plt and underscores the necessity of closely monitoring Plt levels in the postop period. Furthermore, the results of this study are aligned with previous research indicating that lower Plt is associated with higher mortality risk in stroke patients and the activation of the coagulation system. This underscores that Plt is an essential parameter in evaluating thrombotic risks in the postop period.

A high MPV/Plt ratio is considered a risk factor for various

diseases and has been found to be associated with MI, anemia, and hepatocellular carcinoma (9, 36).

In the study conducted by Jin Soo Han and colleagues, the MPV/Plt ratio was also found to be significantly high in patients with DVT (33). Additionally, MPV and Plt are generally inversely related, and similar results were obtained in this study as well (37-39). Therefore, an increased MPV/Plt ratio can be considered indicative of both elevated MPV and low Plt. In the study by Elsayed et al., it was found that patients presenting with cerebrovascular stroke had significantly higher MPV and MPV/Plt ratios compared to the control group (40).

Findings from various studies underscore the importance of monitoring the MPV/Plt ratio in the postop period. Given the elevated thrombotic risks during this time, an increasing MPV/Plt ratio can provide clinicians with critical information regarding a patient's predisposition to thrombotic complications. Regular monitoring of the MPV/Plt ratio not only assists in assessing thrombosis risk but also enables timely intervention to mitigate this risk. For instance, in patients with a high MPV/Plt ratio, it may be necessary to initiate antithrombotic treatments earlier or to review and adjust current treatment plans.

Furthermore, monitoring the MPV/Plt ratio can contribute to developing more personalized treatment approaches based on individual patient risk profiles, potentially improving postop outcomes and helping prevent serious complications. In conclusion, evaluating MPV, Plt, and the MPV/Plt ratio in patients following TKA provides valuable information for preventing and managing postop complications. Incorporating these parameters into routine clinical practice may significantly enhance patient monitoring by more accurately assessing risk profiles and optimizing treatment strategies. This enables early detection of thrombotic risks and timely intervention during the postoperative period, thereby improving patient safety and helping to prevent serious complications. Such an approach could be a critical advancement in optimizing patient follow-up and identifying potential complications early in the period following TKA.

Limitations of the Study

This study has several significant limitations. First, due to its retrospective design, the collection process may need to include more accurate data. Second, the research was conducted at a single center, which may limit the generalizability of the findings. More comprehensive results could be obtained with data from different centers and populations. Third, the patients were only monitored during the short-term postoperative period. There is a lack of information on long-term thrombotic complications or other postoperative outcomes, which poses a limitation in evaluating the long-term effects of the findings.

CONCLUSION

This study demonstrates an increase in MPV and MPV/Plt ratio and a decrease in Plt following TKA. These changes may be indicative of an elevated thrombotic risk. Therefore, regularly monitoring these parameters after TKA is crucial for the early detection and management of potential complications. However, these findings need to be validated through more extensive research involving a larger patient cohort and long-term follow-up.

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: Ethical approval for the study was obtained from the Ethics Committee of KTO Karatay University on October 14, 2024 (Decision No: E-41901325-200-95694). The research was carried out in accordance with the Declaration of Helsinki and relevant ethical principles.

Athorship Contributions: Concept: EK, YT, AM, NAE, MHS, BK, AY, Design: EK, YT, AM, NAE, MHS, BK, AY, Supervising: EK , Financing and equipment: EK, Data collection and entry: EK, YT, AM, NAE, MHS, BK, AY, Analysis and interpretation: EK, YT, NAE, MHS, BK, AY, Literature search: EK, Writing: EK, AM, MHS, Critical review: EK, YT, AM, NAE, MHS, AY.

REFERENCES

1. Zuckerman JD. Inpatient rehabilitation after total joint replacement. JAMA. 1998;279(11):880. doi: 10.1001/jama.279.11.880.
2. Harris WH, Sledge CB. Total hip and total knee replacement. JNEJoM. 1990;323(11):725-31. doi: 10.1056/NEJM199009133231106.
3. Liang MH, Cullen KE, Larson MG, Thompson MS, Schwartz JA, Fossel AH, et al. Cost-effectiveness of total joint arthroplasty in osteoarthritis. 1986;29(8):937-43. Arthritis Rheum. doi: 10.1002/art.1780290801.
4. Yuri Gasparyan A, Ayvazyan LP, Mikhailidis DD, Kitas G. Mean platelet volume: a link between thrombosis and inflammation. Curr Pharm Des? 2011;17(1):47-58. doi: 10.2174/138161211795049804.

5. Gasparyan AY, Stavropoulos-Kalinoglou A, Toms TE, Douglas KM, Kitas G, Targets AD. Association of mean platelet volume with hypertension in rheumatoid arthritis. Inflamm Allergy Drug Targets. 2010;9(1):45-50. doi: 10.2174/187152810791292854.

6. Chu S, Becker R, Berger P, Bhatt D, Eikelboom J, Konkle B, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010;8(1):148-56. doi: 10.1111/j.1538-7836.2009.03584.x.

7. Hou Y, Carrim N, Wang Y, Gallant RC, Marshall A, Ni H. Platelets in hemostasis and thrombosis: Novel mechanisms of fibrinogen-independent platelet aggregation and fibronectin-mediated protein wave of hemostasis. J Biomed Res. 2015;29(6):437. doi: 10.7555/JBR.29.20150121.

8. Chu H, Chen WL, Huang CC, Chang HY, Kuo HY, Gau CM, et al. Diagnostic performance of mean platelet volume for patients with acute coronary syndrome visiting an emergency department with acute chest pain: the Chinese scenario. Emerg Med J. 2011; 28(7):569-74. doi: 10.1136/emj.2010.093096.

9. Azab B, Torbey E, Singh J, Akerman M, Khoueiry G, Mcginn JT, et al. Mean platelet volume/platelet count ratio as a predictor of long-term mortality after non-ST-elevation myocardial infarction. Platelets. 2011;22(8):557-66. doi: 10.3109/09537104.2011.584086.

10. Cho SY, Yang JJ, Suh J-T, Lee W-I, Lee HJ, Park TS. Mean platelet volume/platelet count ratio in anemia. Platelets. 2013;24(3):244-5. doi: 10.3109/09537104.2012.684734.

11. Colkesen Y, Muderrisoglu H. medicine l. The role of mean platelet volume in predicting thrombotic events. Clin Chem Lab Med. 2012;50(4):631-4. doi: 10.1515/CCLM.2011.806.

12. Thompson CB, Jakubowski JA, Quinn PG, Deykin D, Valeri CR. Platelet size as a determinant of platelet function. J Lab Clin Med. 1983;101(2):205-13.

13. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019;2019(1):9213074. doi: 10.1155/2019/9213074.

14. Ranjith M, Divya R, Mehta V, Krishnan M, KamalRaj R, Kavishwar A. Significance of platelet volume indices and platelet count in ischaemic heart disease. J Clin Pathol. 2009;62(9):830-3. doi: 10.1136/jcp.2009.066787.

15. Ates S, Oksuz H, Dogu B, Bozkus F, Ucmak H, Yanıt F. Can mean platelet volume and mean platelet volume/platelet count ratio be used as a diagnostic marker for sepsis and systemic inflammato ry response syndrome? Saudi Med J. 2015;36(10):1186. doi: 10.15537/smj.2015.10.10718.

16. Kageyama K, Nakajima Y, Shibasaki M, Hashimoto S, Mizobe T. Haemostasis. Increased platelet, leukocyte, and endothelial cell activity are associated with increased coagulability in patients after total knee arthroplasty. J Thromb Haemost. 2007;5(4):738-45. doi: 10.1111/j.1538-7836.2007.02443.x.

17. Aliosmanoglu I, Gul M, Oguz A, Basol O, Uslukaya O, Keles C, et al. Can mean platelet volume be a new risk factor in portal venous thrombosis? Clin Appl Thromb Hemost. 2013;19(4):433-6. doi: 10.1177/1076029612464903.

18. Butterworth R, Bath PM. The relationship between mean platelet volume, stroke subtype and clinical outcome. Platelets.1998;9(6):359-64.doi:10.1080/09537109876429.

19. Cameron H, Phillips R, Ibbotson R, Carson PH. Platelet size in myocardial infarction. Br Med J (Clin Res Ed). 1983;287(6390):449-51. doi: 10.1136/bmj.287.6390.449.

20. Kiliçli-Çamur N, Demirtunç R, Konuralp C, Eskiser A, Başaran Y. Could mean platelet volume be a predictive marker for acute myocardial infarction? Med Sci Monit. 2005;11(8):392.

21. Bath P, Algert C, Chapman N, Neal B. Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke. 2004;35(3):622-6. doi: 10.1161/01.STR.0000116105.26237.EC.

22. Braekkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Størmer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromsø study. J Thromb Haemost. 2010;8(1):157-62. doi: 10.1111/j.1538-7836.2009.03498.x.

23. Çil H, Yavuz C, İslamoğlu Y, Tekbaş EÖ, Demirtaş S, Atılgan ZA, et al. Platelet count and mean platelet volume in patients with in-hospital deep venous thrombosis. Clin Appl Thromb Hemost. 2012;18(6):650-3. doi: 10.1177/1076029611435838.

24. Endler G, Klimesch A, Sunder-Plassmann H, Schillinger M, Exner M, Mannhalter C, et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol. 2002;117(2):399-04. doi: 10.1046/j.1365-2141.2002.03441.x.

25. O'malley T, Langhorne P, Elton R, Stewart C. Platelet size in stroke patients. Stroke. 1995;26(6):995-9. doi:

10.1161/01.str.26.6.995.

26. Mutlu H, Artış TA, Erden A, Akca Z. thrombosis/hemostasis a. Alteration in mean platelet volume and platicrit values in patients with cancer that developed thrombosis. Clin Appl Thromb Hemost. 2013;19(3):331-3. doi: 10.1177/1076029611433644.
27. Icli A, Aksoy F, Turker Y, Uysal BA, Alpay MF, Dogan A, et al. Relationship between mean platelet volume and pulmonary embolism in patients with deep vein thrombosis. Heart Lung Circ. 2015;24(11):1081-6. doi: 10.1016/j.hlc.2015.04.170.
28. Gulcan M, Varol E, Etli M, Aksoy F, Kayan M. Mean platelet volume is increased in patients with deep vein thrombosis. Clin Appl Thromb Hemost. 2012;18(4):427-30. doi: 10.1177/1076029611427437.
29. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. Hematology Am Soc Hematol Educ Program. 2010;2010(1):135-43. doi: 10.1182/asheducation-2010.1.135.
30. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med. 1995;332(20):1330-6. doi: 10.1056/NEJM199505183322003.
31. Skeith L, Baumann Kreuziger L, Crowther MA, Warkentin TE. A practical approach to evaluating postoperative thrombocytopenia. Blood Adv. 2020;4(4):776-83. doi: 10.1182/bloodadvances.2019001414.
32. D'erasmo E, Aliberti G, Celi F, Romagnoli E, Vecci E, Mazzuoli GF. Platelet count, mean platelet volume and their relation to prognosis in cerebral infarction. J Intern Med. 1990;227(1):11-4. doi: 10.1111/j.1365-2796.1990.tb00111.x.
33. Han JS, Park TS, Cho SY, Joh JH, Ahn HJ. Increased mean platelet volume and mean platelet volume/platelet count ratio in Korean patients with deep vein thrombosis. Platelets. 2013;24(8):590-3. doi: 10.3109/09537104.2012.748187.
34. Glud T, Schmidt EB, Kristensen SD, Arnfred T. Platelet number and volume during myocardial infarction in relation to infarct size. Acta Med Scand. 1986;220(5):401-5. doi: 10.1111/j.0954-6820.1986.tb02787.x.
35. Fagher B, Sjögren A, Sjögren U. Platelet counts in myocardial infarction, angina pectoris and peripheral artery disease. Acta Med Scand. 1985;217(1):21-6. doi: 10.1111/j.0954-6820.1985.tb01629.x.
36. Cho SY, Yang JJ, You E, Kim B-H, Shim J, Lee HJ, et al. Mean platelet volume/platelet count ratio in hepatocellular carcinoma. Plateletes. 2013;24(5):375-7. doi: 10.3109/09537104.2012.701028.
37. David Bessman J, Williams LJ, Ridgway Gilmer Jr. Mean platelet volume. The inverse relation of platelet size and count in normal subjects, and an artifact of other particles. Am J Clin Pathol. 1981;76(3):289-93. doi: 10.1093/ajcp/76.3.289.
38. Lamparelli R, Baynes RD, Atkinson P, Bezwoda WR, Mendelow BV. Platelet parameters-Part I.-Platelet counts and mean platelet volume in normal pregnant subjects. S Afr Med J. 1988;73(1):36-9.
39. Lozano M, Narvaez J, Faundez A, Mazzara R, Cid J, Jou J, et al. Platelet count and mean platelet volume in the Spanish population. Med Clin (Barc). 1998;110(20):774-7.
40. Elsayed AM, Mohamed GA. Mean platelet volume and mean platelet volume/platelet count ratio as a risk stratification tool in the assessment of severity of acute ischemic stroke. Alexandria Journal of Medicine. 2017;53(1):67-70. doi: 10.1016/j.ajme.2016.03.003.

CASE REPORT
DOI: 10.17944/interdiscip.1569484
Interdiscip Med J 2025;16(54):56-59

Metformin-associated lactic acidosis and acute kidney injury

Can Huzmeli

Hatay Education and Research Hospital, Department of Nephrology, Hatay, Türkiye

Abstract

Diabetes mellitus is a common disease worldwide. Metformin is included in the first-line treatment of type 2 diabetes mellitus. Metformin-associated lactic acidosis (MALA) is rare but can be life-threatening. In this case report, MALA and acute kidney injury (AKI) were detected in a 74-year-old female patient who presented with impaired consciousness. The patient was treated with hydration and hemodialysis (HD). MALA diagnosis was based on metformin levels > 5 mg/L, decreased pH, low bicarbonate levels, lactate levels > 5 mmol/L, and increased anion gap.

Keywords: Diabetes mellitus, metformin, lactic acidosis, acute kidney injury

INTRODUCTION

Diabetes Mellitus is one of the non-communicable diseases with an increasing global prevalence. Over the past few decades, the incidence of diabetes mellitus has risen sharply worldwide. It currently affects an estimated 537 million adults aged between 20 and 79 globally. It is estimated that by 2030, 643 million people will have diabetes mellitus, and this number is expected to rise to 783 million by 2045. Patients with diabetes mellitus may experience symptoms ranging from unexpected weight loss to increased urination, thirst, and hunger (1). The diagnosis of type 2 diabetes mellitus is made when one of the following criteria is present: fasting blood glucose ≥ 126 mg/dL, glycated hemoglobin A1c ≥ 6.5%, or postprandial glucose ≥ 200 mg/dL. Metformin is an antidiabetic drug that, in addition to its potential efficacy in lowering blood sugar levels, has beneficial effects on body weight, plasma lipids, and the risk of microvascular and macrovascular complications (2).

Metformin controls blood glucose levels by reducing gluconeogenesis and inhibiting glycogen breakdown. Additionally, it prevents hyperglycemia by decreasing glucose absorption from the gastrointestinal system and enhancing insulin signaling and glucose utilization. Metformin is generally considered safe and well-tolerated. However, gastrointestinal side effects such as diarrhea, nausea, and vomiting are relatively common and can affect up to 30% of patients using metformin. Less commonly, some patients may experience chest discomfort, headaches, sweating, hypoglycemia, weakness, and rhinitis while on metformin. Metformin may cause vitamin B12 deficiency in the long term. Metformin overdose has been linked to hypoglycemia and lactic acidosis (3-4).

This article presents a case report discussing metformin intoxication in a patient followed up with a diagnosis of diabetes mellitus.

CASE

A 74-year-old female patient was admitted to the emergency department with impaired consciousness. Her medical history included diabetes mellitus and hypertension, for which she was taking gliclazide, metformin, olmesartan, and hydrochlorothiazide. On physical examination, her general condition was poor, she was confused, uncooperative, drowsy, and her blood pressure was 100/60 mmHg with a heart rate of 107 bpm. Other physical examinations were normal. Laboratory investigations revealed glucose of 46 mg/dL, blood urea nitrogen (BUN) of 70 mg/dL, serum creatinine of 6.8 mg/dL, sodium of 148 mmol/L, potassium of 6.4 mmol/L, and hemoglobin of 10.4 g/dL. Due to anuria, a urine test could not be performed. Arterial blood gas analysis demonstrated

Cite this article: Huzmeli C. Metformin-associated lactic acidosis and acute kidney injury. Interdiscip Med J. 2025;16(54):56-59. https://doi.org/10.17944/interdiscip.1569484

Corresponding Author: Dr. Can Huzmeli, Hatay Education and Research Hospital, Department of Nephrology, Hatay, Türkiye
E mail: chuzmeli@hotmail.com
ORCID iD:0000-0002-5499-4886

Received: Oct 17, 2024
Accepted: Dec 30, 2024

a pH of 7.15, PCO2 of 34 mmHg, HCO3 of 12 mEq/L, lactate level of 7.3 mmol/L, and an anion gap of 17 mEq/L.

The patient was suspected of having MALA and acute kidney injury (AKI). She was treated in the emergency department with 20% dextrose for hypoglycemia and hydration for lactic acidosis. Active charcoal was administered for MALA. Additionally, sodium bicarbonate replacement was initiated due to a pH <7.2 and the presence of AKI. The patient was admitted to the intensive care unit (ICU). In the ICU, repeat blood gas analysis revealed a pH of 7.11, PCO2 of 25 mmHg, HCO3 of 8.1 mEq/L, and a lactate level of 9.8 mmol/L. Despite normalization of glucose levels, the patient's altered mental status persisted, and she remained drowsy.

The patient underwent hemodialysis (HD) for MALA and AKI, and hydration therapy was continued. After HD, her mental status improved. On the first day, blood gas analysis demonstrated a pH of 7.2, PCO2 of 24 mmHg, HCO3 of 11 mEq/L, and a lactate level of 2.4 mmol/L. Due to persistent AKI, blood gas abnormalities, and oliguria, she underwent a second HD session. A total of two HD sessions were performed. On the second day, urine output was adequate, and blood gas analysis normalized, so further HD was not required. The patient's serum creatinine level decreased to 1.3 mg/dl on the 5th day. At a follow-up clinic visit one week later, her renal function had returned to normal.

DISCUSSION

Metformin is a commonly used antidiabetic medication for patients with type 2 diabetes mellitus. The therapeutic plasma concentration of metformin is known to be <2mg/L (the maximum therapeutic concentration of metformin is between 1.5 and 3 mg/L), with peak levels reached 4 to 8 hours after absorption and an elimination half-life of 18 hours. MALA is a serious complication defined by blood lactate levels >5 mmol/L, blood metformin levels >5 mg/L, decreased pH, decreased bicarbonate, and increased anion gap. The incidence of MALA is estimated to range between 1 and 9 per 100,000 individuals. Lactate levels increase due to either overproduction or reduced clearance. MALA occurs due to decreased metformin clearance, renal dysfunction, decreased lactate clearance in liver disorders, and/or increased lactate production (e.g., in sepsis, congestive heart failure, respiratory failure, acute myocardial infarction, decreased tissue perfusion, or anoxia). Although metformin is not contraindicated in dehydration, shock, alcohol consumption, or hypoxic states, these conditions increase the risk of lactic acidosis. MALA can also develop in patients with even mild renal dysfunction (5-9).

Severe toxicity, such as MALA, can occur during critical illness due to metformin accumulation. It causes mitochondrial dysfunction through the inhibition of oxidative phosphorylation by metformin. Therefore, it causes lactic acidosis even in the presence of oxygen. This dysfunction affects multiple tissues, including the liver, skeletal muscles, heart, kidneys, and platelets. Metformin is absorbed primarily in the small intestine, binds negligibly to proteins in the blood, undergoes minimal metabolism, and is excreted unchanged by the kidneys (9). The most serious side effect of metfomin is lactic acidosis. MALA and metformin-induced lactic acidosis (MILA) remain controversial topics, as they are two distinct conditions with different origins and prognoses. Measuring plasma metformin concentration can aid in diagnosing MILA or MALA. In one study, 173 patients (109 MILA, 64 MALA) were included. MALA patients more frequently experienced shock, and mortality was associated with underlying conditions, with metformin accumulation exacerbating lactic acidosis. The mortality rate was 26% for MALA and 7% for MILA. HD patients had a higher mortality rate and a higher prevalence of sepsis (10).

Kim and colleagues evaluated metformin levels in 107 patients, 19 (17.8%) of whom met MALA diagnostic criteria. Among these MALA patients, 15 (78.9%) had AKI, and 4 (21.1%) had end-stage renal disease (ESRD). Sixteen patients received renal replacement therapy, with 9 undergoing intermittent HD, 4 receiving continuous renal replacement therapy, and 3 receiving both treatments sequentially. The mortality rate was 36.8% (11).

AKI associated with MALA is rare but well-documented. In one study, all patients with MALA also had AKI. In this study, it was suggested that AKI was triggered by dehydration resulting from vomiting and diarrhea due to metformin toxicity. In addition, plasma lactate levels increase with AKI and the risk of lactic acidosis increases. (12). In a case study of a 70-year-old female patient with type 2 diabetes mellitus, MALA was diagnosed, and AKI and hyperkalemia prompted treatment with renal replacement therapy. This patient was also found to be COVID-19 positive (13). Ariga and colleagues reported a case of a 60-year-old male patient diagnosed with MALA and AKI who was taking a normal dose of metformin. The patient presented with complaints of dizziness, malaise, and oliguria. In addition, metformin levels were found to be high in this patient (14).

In the treatment of the patient, metformin therapy was discontinued, 20% dextrose was administered for hypoglycemia, and hydration was initiated. The patient underwent HD due to anuric AKI and lactic acidosis. After two sessions of HD, the patient was not subjected to further sessions due to the presence of urine output and a downward

trend in serum creatinine levels. The management of MALA is controversial and is largely supportive. Treatment options include hydration, activated charcoal, sodium bicarbonate, HD, or continuous venovenous hemofiltration. Early administration of activated charcoal may be considered. Contraindications to activated charcoal include bowel obstruction, perforation, hypotension, or reduced bowel motility. Severe acidosis is treated with sodium bicarbonate infusion, although the use of sodium bicarbonate replacement remains debated. However, sodium bicarbonate replacement should be considered in patients with a pH <7.15. Bicarbonate replacement is recommended for pH < 7.20 in cases of cardiovascular disease and/or hemodynamic instability in the patient. Hypotension and shock should be managed with intravenous crystalloids and vasopressors as needed. Intermittent HD and continuous renal replacement therapy are effective in treating MALA, although documentation is limited to a few case series and reports worldwide. The Extracorporeal Treatment in Poisoning (EXTRIP) workgroup recommends initiating HD in cases with pH ≤7.0, lactate >20 mmol/L, and/or the presence of shock, acute or chronic renal or liver failure, or altered mental status. HD can be discontinued once lactate levels drop below 3 mmol/L and pH reaches 7.35 (5,6,15-17). The mortality rate associated with MALA ranges from 30% to 50% (18).

CONCLUSION

Patients with type 2 diabetes mellitus who are using metformin should be closely monitored for the risk of MALA and AKI. If risk factors for MALA are present, metformin use should be discontinued or paused. Although MALA is rare, it carries a high mortality rate.

ACKNOWLEDGEMENT

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Thanks: I would like to thank the Intensive Care and Nephrology service nurses for their close monitoring of the patient.

REFERENCES

1. Perveen W, Ahsan H, Shahzad R, Fayyaz S, Zaif A, Paracha MA, Alghadir AH. Prevalence of peripheral neuropathy, amputation, and quality of life in patients with diabetes mellitus. Scientific Reports, 2024;14(1):14430. https://doi.org/10.1038/s41598-024-65495-2
2. Song A, Zhang C, Meng X. Mechanism and application of metformin in kidney diseases: An update. Biomedicine & Pharmacotherapy, 2021;138:111454. https://doi.org/10.1016/j.biopha.2021.111454.
3. Aldobeaban S, Mzahim B and Alshehri AA. Recurrent hypoglycemia secondary to metformin toxicity in the absence of co-ingestions: a case repor, JMCR 2018; 12:223. https://doi.org/10.1186/s13256-018-1758-0
4. Metformin. Calette Corcoran; Tibb F. Jacobs. StatPearls Publishing; 2024
5. Dyatlova N, Tobarran NV, Kannan L, North R, Wills BK. Metformin associated lactic acidosis (MALA). 2022.
6. Simon EL, Sherry AC, Rabinowitz J. Metformin-Associated Lactic Acidosis-Is This on Your Radar?. JEM, 2024;66(4): e530-e533. https://doi.org/10.1016/j.jemermed.2023.11.017
7. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabol, 2016;65(2): 20-29. https://doi.org/10.1016/j.metabol.2015.10.014.
8. Di Mauro S, Filippello A, Scamporrino A, Purrello F, Piro S, Malaguarnera R. Metformin: when should we fear lactic acidosis?. Int. J. Mol. Sci, 2022;23(15):8320. https://doi.org/10.3390/jms23158320
9. See KC. Metformin-associated lactic acidosis: A mini review of pathophysiology, diagnosis and management in critically ill patients. WJD, 2024;15(6):1178. https://doi.org/10.4239/wjd.v15.i6.1178
10. Corchia A, Wynckel A, Journet J, Moussi Frances J, Skandrani N, Lautrette A, Rieu P. Metformin-related lactic acidosis with acute kidney injury: results of a French observational multicenter study. Clinical Toxicology, 2020;58(5): 375-382. https://doi.org/10.1080/15563650.2019.1648816
11. Kim S, Sarwal A, Yee XT, Fraga SAG, Campion V, Gnanasekaran I. Metformin-associated lactic acidosis (MALA): Is it an underestimated entity? A retrospective, single-center case series. Hemodialysis International,

2024;28(1):32-39. https://doi.org/10.1111/hdi.13113

12. Goonoo MS, Morris R, Raithatha A, Creagh F. Metformin-associated lactic acidosis: reinforcing learning points. DTB, BMJ, 2020;13(9): e235608. https://doi.org/10.1136/dtb.2021.235608rep
13. Vordoni A, Theofilis P, Vlachopanos G, Koukoulaki M, Kalaitzidis RG. Metformin-associated lactic acidosis and acute kidney injury in the era of COVID-19. Frontiers in Bioscience-Scholar, 2021;13(2):202-207. https://doi.org/10.52586/S563.
14. Ariga M, Hagita J, Soda M, Oida Y, Teramachi H, Kitaichi K. Daily dose of metformin caused acute kidney injury with lactic acidosis: a case report. JMCR, 2023;17(1): 393. https://doi.org/10.1186/s13256-023-04136-0
15. Alotaibi M, Ali F, Leung S, Kent R. Metformin Induced Lactic Acidosis What Is the Effective Treatment?. OJNeph, 2020;10(1): 11-17. https://doi.org/10.4236/ojneph.2020.101002
16. Wills BK, Bryant SM, Buckley P, Seo B. Can acute overdose of metformin lead to lactic acidosis? Am J Emerg Med. 2010;28(8):857-861. https://doi.org/10.1016/j.ajem.2009.04.012
17. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, Hoffman RS, Nolin TD, Ghannoum M., Extracorporeal Treatments in Poisoning Workgroup. Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med. 2015;43(8):1716-1730. https://doi.org/10.1097/ccm.0000000000001002
18. Eppenga WL, Lalmohamed A, Geerts AF, Derijks HJ, Wensing M, Egberts A, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. Diabetes Care. 2014;37(8):2218–2224. https://doi.org/10.2337/dc13-3023

CASE REPORT
DOI: 10.17944/interdiscip.1604033
Interdiscip Med J 2025;16(54):60-62

Treatment of hemorrhagic right gastro-omental artery pseudoaneurysm via ultrasound-guided percutaneous thrombin injection

Ibrahim Bariscan Soydan[1], Alperen Kayali[2]

[1] Hatay Education and Research Hospital, Department of Radiology, Hatay, Türkiye
[2] Baskent University Konya Application and Research Center, Department of Radiology, Konya, Türkiye

Abstract

Visceral artery pseudoaneurysms are life-threatening conditions due to their high risk of rupture and hemorrhage. Traditional treatments include endovascular interventions such as stent grafting and embolization, or open surgery. However, ultrasound-guided percutaneous thrombin injection is rarely used as a first-line therapy. This case report presents a 66-year-old patient with an iatrogenic hemorrhagic pseudoaneurysm of the right gastro-omental artery, successfully treated with ultrasound-guided percutaneous thrombin injection. Under local anesthesia, a 5 mL bolus of thrombin was injected into the pseudoaneurysm sac, resulting in immediate thrombosis confirmed by ultrasound and Doppler imaging. The patient demonstrated stable hemodynamics and hemoglobin levels post-procedure. Follow-up imaging showed significant regression of hemorrhagic fluid and no contrast extravasation. This case highlights ultrasound-guided thrombin injection as a safe, cost-effective, and radiation-free alternative to traditional treatments for selected visceral artery pseudoaneurysms, particularly in distal branches or emergency settings.
Keywords: Visceral artery, pseudoaneurysm, ultrasonography, minimally invasive procedures

INTRODUCTION

Visceral artery pseudoaneurysms are associated with a high risk of rupture and hemorrhage, necessitating timely and effective management (1). Standard treatment options, including endovascular techniques such as stent grafting or embolization, and open surgical repair, are well-established but present certain limitations. These include exposure to ionizing radiation, relatively high costs, and potential complications, particularly in high-risk or hemodynamically unstable patients (2). Moreover, these approaches may be less suitable for small pseudoaneurysms, or lesions located in distal arterial branches due to technical challenges. Ultrasound-guided percutaneous thrombin injection, in contrast, offers a minimally invasive, cost-effective, and radiation-free alternative that addresses some of these limitations. Despite its potential benefits, this technique is rarely employed as a first-line treatment in clinical practice. This report presents the case of a 66-year-old patient with an iatrogenic hemorrhagic pseudoaneurysm of the right gastro-omental artery, successfully treated with ultrasound-guided percutaneous thrombin injection. The implications of this technique are discussed in the context of the presented case and existing literature.

CASE

A 66-year-old patient underwent cholecystectomy and surgical drainage for an intraperitoneal abscess. Postoperatively, the patient experienced a significant drop in hemoglobin levels. Contrast-enhanced CT revealed contrast extravasation from the distal gastroduodenal branch, extending to the right gastro-omental artery, with associated hemorrhagic fluid accumulation around the stomach. Ultrasound examination identified a pseudoaneurysm measuring 10.5 × 11.5 mm in the subxiphoid region. Given the pseudoaneurysm's accessibility, ultrasound-guided

Cite this article: Soydan IB, Kayali A. Treatment of hemorrhagic right gastro-omental artery pseudoaneurysm via ultrasound-guided percutaneous thrombin injection. Interdiscip Med J 2025;16(54):60-62. https://doi.org/10.17944/interdiscip.1604033

Corresponding Author: Dr. Ibrahim Bariscan Soydan, Hatay Education and Research Hospital, Department of Radiology, Hatay, Türkiye
Email: barissoydan35@gmail.com
ORCID iD: 0000-0001-9640-7881

Received: Dec 19, 2024
Accepted: Jan 11, 2025

percutaneous thrombin injection was selected as the treatment modality.

Under ultrasound guidance and local anesthesia, a 5F amniocentesis needle (5 French gauge needle) was percutaneously advanced into the aneurysm sac (Figure 1). A single 5 mL bolus of thrombin (1,000 U/mL) was injected. Real-time ultrasound and Doppler imaging confirmed successful thrombosis of the pseudoaneurysm (Figure 2). The procedure was well-tolerated, with no complications. Post-procedure, the patient demonstrated stabilized hemodynamics and hemoglobin levels.

A CT angiogram performed on the third postoperative day showed no progression of hemorrhagic fluid and no contrast extravasation (Figure 3). Follow-up imaging on the 14th day revealed significant regression of the hemorrhagic fluid and no evidence of pseudoaneurysm recurrence.

DISCUSSION

Ultrasound-guided percutaneous thrombin injection is a minimally invasive, safe, and effective technique for managing visceral artery pseudoaneurysms. It provides a radiation-free and cost-effective alternative to endovascular methods, particularly for small aneurysms or distal arterial branches. Previous studies have reported the successful use of thrombin injection in pseudoaneurysms of the pancreaticoduodenal artery, splenic artery, renal-intrarenal artery, superior mesenteric artery, and uterine arteries (3-8). For instance, Barbiero et al. reported successful treatment of a pancreaticoduodenal artery pseudoaneurysm using this technique (3). Similarly, Krueger et al. highlighted its effectiveness in managing a splenic artery pseudoaneurysm (4). Benjaminov and Atri demonstrated successful thrombin injection in an intrarenal pseudoaneurysm (5), while Ros et al. described its utility in uterine artery pseudoaneurysms (8).

A study involving 19 visceral artery pseudoaneurysms highlighted higher success rates for thrombin injection in pseudoaneurysms smaller than 23 mm, particularly those located in distal branches (9). This case highlights the effectiveness of percutaneous thrombin injection as a viable alternative, especially for selected patients in emergency settings or when conventional methods are unsuitable.

CONCLUSION

Ultrasound-guided percutaneous thrombin injection offers a safe, effective, and minimally invasive option for treating visceral artery pseudoaneurysms. This method is particularly beneficial for patients with pseudoaneurysms in distal branches or in cases where endovascular treatments are contraindicated. Further studies are needed to establish standardized protocols and assess long-term outcomes.

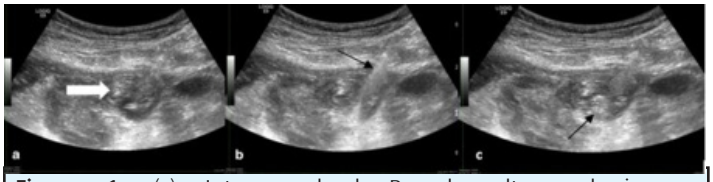

Figure 1. (a) Intra-procedural B-mode ultrasound images: pseudoaneurysm sac prior to thrombin injection (white arrow), (b) advancement of the needle (black arrow) into the pseudoaneurysm sac, and (c) echogenic primary thrombus formation (black arrow) within the pseudoaneurysm sac following the thrombin injection

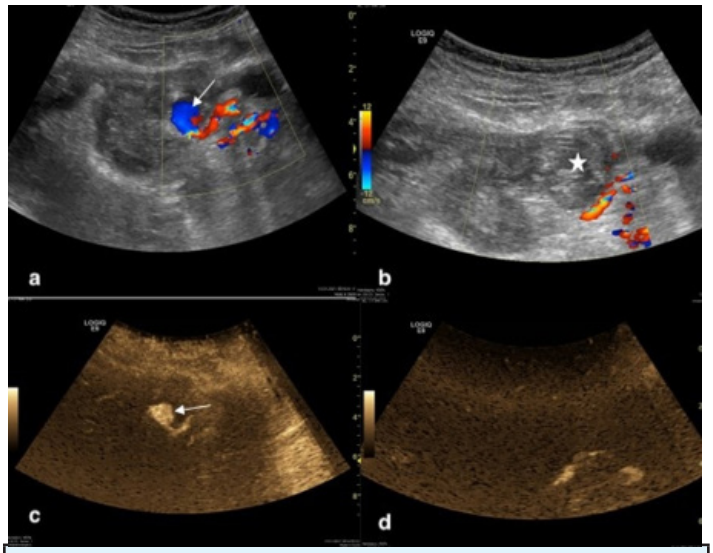

Figure 2. (a) Pre-procedural doppler ultrasound imaging demonstrates vascular flow within the pseudoaneurysm sac (white arrow). (b) Post-procedural doppler ultrasound imaging reveals the absence of vascular flow within the pseudoaneurysm sac (white star). (c) Pre-procedural B-flow imaging clearly depicts the pseudoaneurysm neck and sac (white arrow). (d) Post-procedural B-flow imaging confirms the absence of blood flow into the pseudoaneurysm sac

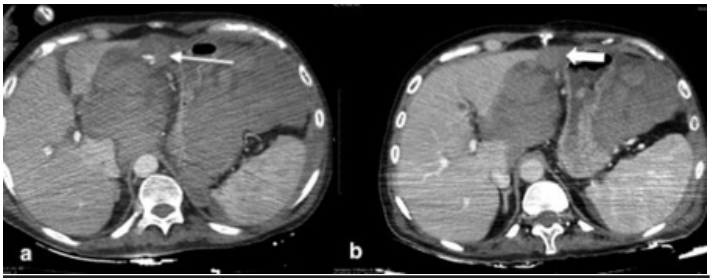

Figure 3. Computed tomography (CT) images before and after the procedure: (a) Pre-procedural CT showing the pseudoaneurysm sac with active extravasation (indicated by the arrow). (b) Post-procedural CT demonstrating the successful cessation of extravasation into the pseudoaneurysm sac (white arrow)

ACKNOWLEDGEMENTS

Peer-Review: Both externally and internally peer reviewed.

Conflict of Interest: The authors declare that they have no conflict of interests regarding content of this article.

Financial Support: The Authors report no financial support regarding content of this article.

Ethical Declaration: Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Athorship Contributions: Concept: IS, AK, Design: IS, AK, Supervising: AK, Data collection and entry: IS, AK, Analysis and interpretation: IS, AK, Literature search: IS, Writing: IS, Critical review: IS, AK

REFERENCES

1. Madhusudhan KS, Venkatesh HA, Gamanagatti S, Garg P, Srivastava DN. Interventional Radiology in the Management of Visceral Artery Pseudoaneurysms: A Review of Techniques and Embolic Materials. Korean J Radiol. 2016;17(3):351-63. https://doi.org/10.3348/kjr.2016.17.3.351
2. Sessa C, Tinelli G, Porcu P, Aubert A, Thony F, Magne JL. Treatment of visceral artery aneurysms: description of a retrospective series of 42 aneurysms in 34 patients. Ann Vasc Surg. 2004;18(6):695-703. https://doi.org/10.1007/s10016-004-0112-8.
3. Barbiero G, Battistel M, Susac A, Miotto D. Percutaneous thrombin embolization of a pancreatico-duodenal artery pseudoaneurysm after failing of the endovascular treatment. World J Radiol. 2014;6(8):629-35. https://doi.org/10.4329/wjr.v6.i8.629.
4. Krueger K, Zaehringer M, Lackner K. Percutaneous treatment of a splenic artery pseudoaneurysm by thrombin injection. J Vasc Interv Radiol. 2005;16(7):1023-5. https://doi.org/10.1097/01.RVI.0000162167.54455.C0.
5. Benjaminov O, Atri M. Percutaneous thrombin injection for treatment of an intrarenal pseudoaneurysm. AJR Am J Roentgenol. 2002;178(2):364-6. https://doi.org/10.2214/ajr.178.2.1780364.
6. Casey P, Kausar A, Gavan D, Wilde N. Ultrasound-guided percutaneous thrombin for the management of superior mesenteric artery pseudoaneurysm. J Vasc Surg Cases. 2015;1(3):211-3. https://doi.org/10.1016/j.jvsc.2015.06.001.
7. Siu YP, Tong MK, Leung KT, Kwan TH, Au TC, Cheung YK, Luk SH. Renal artery pseudoaneurysm following renal transplantation and treatment by percutaneous thrombin injection. Hong Kong Med J. 2006;12(1):80-1.
8. Ros C, Barnes D, Fervienza A, Oses G, Alcázar JL, Martínez-Román S, Rovirosa À, Carmona F, Gómez F. Ultrasound-guided transvaginal thrombin injection of uterine arteries pseudoaneurysms. Br J Radiol. 2017;90(1074):20160913. https://doi.org/10.1259/bjr.20160913.
9. Gorsi U, Agarwal V, Yaser M, Kalra N, Chaluvashetty S, Kang M, Lal A, Sandhu MS. Utility of percutaneous thrombin injection for treating visceral pseudoaneurysms. Minim Invasive Ther Allied Technol. 2021;30(3):174-8. https://doi.org/10.1080/13645706.2020.1720251.