Year August 2024
Volume 15
Issue 52

INTERDISCIPLINARY MEDICAL JOURNAL

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2024;15(52)

EDITORIAL BOARD

Institutional Contact

E-mail: tip.dergi@mku.edu.tr
Hatay Mustafa Kemal University, 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

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INDEXED BY

TUBITAK TR INDEX

Türkish Medline

Turkish Citation Index

DOAJ

Index Copernicus World of Journals

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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 15, Issue 52, August 2024

Owner: Dean, Prof. Dr. Cahit Özer on behalf of Hatay Mustafa Kemal University, Faculty of Medicine

Publisher: Hatay Mustafa Kemal University, Faculty of Medicine

Managing Editor: Enver Sedat Borazan

Address: Hatay Mustafa Kemal University, Faculty of Medicine Dean's Office, 31100 Hatay, Türkiye

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

Online Publication Date: September 7, 2024, Hatay

Frequency: Published online three times a year on April, August, and December.

Design and Typesetting: Dr. Uğur Koçak

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2024;15(52)

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, DOAJ 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

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

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.

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.

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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:

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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.

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

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.

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,

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.

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.

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

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.

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.

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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.

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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.

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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.

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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.

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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:

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INTERDISCIPLINARY MEDICAL JOURNAL
Interdiscip Med J 2024;15(52)

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.

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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,

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?

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.

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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.

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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

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.

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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

INTERDISCIPLINARY MEDICAL JOURNAL

Interdiscip Med J 2024;15(52)

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Volume: 15, Issue 52, Year: August 2024

ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1384774
Interdiscip Med J 2024;15(52):37-40

Approach to cases diagnosed with mesenteric panniculitis

Ⓓ **Güven Erdoğrul,** Ⓓ **Güvenç Diner,** Ⓓ **Samed Sayar,** Ⓓ **Sinan Aslan,** Ⓓ **Mustafa Uğur**

Mersin City Education and Research Hospital, Department of General Surgery, Mersin, Türkiye

Abstract

Approach to cases diagnosed with mesenteric panniculitis

Objective: In this study, it was aimed to report the diagnosis, treatment and follow-up results of patients who came to the hospital with complaints of abdominal pain and were diagnosed with Mesenteric Panniculitis (MP) by Abdominal Computed Tomography (ACT).
Method: 32 patients diagnosed with MP by ACT were examined retrospectively. The patients' age, gender, admission leukocyte count, CRP values, comorbidities, medications prescribed at discharge, and relapse status were evaluated.
Results: Of the 32 patients included in the study, 11 were male (34.4%), 21 were female (65.6%), and they had a mean age of 58.75±12.31 years. The average leukocyte value at first admission was 8240±2530 /mm³, CRP average 24.93±47.39 mg/L, neutrophil percentage was not above 80% in any patient. No patients were hospitalized. Recurrence was occurred in 2 (6.25%) patients (after 6 months and 28 months). No malignancy were during follow-up.
Conclusion: MP was diagnosed with ACT. No biopsy was required for diagnosis. Medical treatment was sufficient, no surgical procedure was performed on the patients.
Keywords: Abdominal pain, Computed tomography, Mesenteric Panniculitis

INTRODUCTION

Mesenteric panniculitis (MP) is a rare chronic inflammatory disease of the mesentery (1). Although its etiology is not clear, there are many diseases with which it is associated. Vasculitides, granulomatous diseases, rheumatological diseases, malignancies, pancreatitis, previous abdominal surgery or trauma, ischemic damage and infections are listed as underlying or possibly related conditions (2,3,4).

Prevalence of MP is 0.16-7.8%. MP frequently seen between the ages of 50-60 and is more common in men. In most cases, the small intestinal mesentery is affected. The clinic may vary depending on the stage of the disease (1,2,3).

The most common symptoms are abdominal pain, nausea, vomiting and palpable fullness (1,3). Diagnosis of mesenteric panniculitis is usually set by abdominal computed tomography (ACT) and magnetic resonance imaging without the need for biopsy (5). It was aimed in this study is to determine the follow-up and treatment results of patients diagnosed with Mesenteric panniculitis, a rare cause of abdominal pain.

METHOD

Ethical permission was obtained from the Kahramanmaraş Sütcü İmam University, Medical Faculty Non-Invasive Clinical Research Ethics Committee for this study with date 17.06.2021and number 313.

In this research, 32 patients who were come to the hospital with abdominal pain between September 2014 and June 2021 and were diagnosed with MP on ABT were retrospectively analyzed (Figure1,2).

The data of the patients were obtained from hospital records and in necessary cases patients were contacted via phone. Patients were called in for a check-up every 6 months, and those who did not come for the check-up were contacted by phone. They were invited to the hospital for an examination. Patients who did not come for a follow-up, whose data could not be accessed, and who had additional pathology when diagnosed with MP were excluded from the study. The patients were evaluated in terms of age, gender, first admission leukocyte and CRP values, comorbidities, medical treatment, recurrence and follow-up period.

Cite this article: Erdoğrul G, Diner G, Sayar S, Aslan S, Uğur M. Approach to cases diagnosed with mesenteric panniculitis.. Interdiscip Med J. 2024;15(52):37-40. https://doi.org/10.17944/interdiscip.1384774

Corresponding Author: Dr. Güven Erdoğrul: Mersin City Education and Research Hospital, Department of General Surgery, Mersin, Türkiye
Email: cerraherdogrul@gmail.com
ORCID iD: 0000-0002-9557-7675

Received: Nov 1, 2023
Accepted: Apr 16, 2024

RESULTS

32 patients were evaluated retrospectively, 11 were male (34.4%), 21 were female (65.6%), and they had a mean age of 58.75±12.31 years, follow-up time was 44.31±20.37 months. The average leukocyte value at first admission was 8240±2530 /mm³, CRP average 24.93±47.39 mg/L, neutrophil percentage was not above 80% in any patient (Table.1).

Table 1. Patient Demographics

Gender (Male/Female)		11 M / 21 F
Mean Age (Years)		58.75±12.31
Leukocyte Average		8240±2530 /mm³
CRP Average		24.93±47.39 mg/L
Follow-up period (months)		44.31±20.37
Recurrence		2 (6.25%)

There was no comorbidity in 9 patients. There was one disease in 8 patients, two diseases in 10 patients, and three diseases in 5 patients. 11 patients had type 2 diabetes mellitus and 15 patients had hypertension disease. Trimethoprim-sulfamethoxazole was prescribed to 3 patients, ciprofloxacin was prescribed to 11 patients, amoxicillin-clavulanic acid was prescribed to 3 patients, and only anti-inflammatory was prescribed to 15 patients (Table.2).

Table 2. Medical treatment

Trimethoprim-Sulfamethoxazole	3 (%9,375)
Ciprofloxacin	11 (%34,375)
Amoxicillin-Clavulanic acid	3 (%9,375)
Anti-inflammatory	15 (%46,875)

No patients were hospitalized. Recurrence was occurred in 2 (6.25%) patients (after 6 months and 28 months). In the first treatment of relapsed patients, one was prescribed antibiotic (28 months) and the other was prescribed anti-inflammatory drug (6 months). When the disease recurred, both patients were prescribed only anti-inflammatory drugs and no antibiotics. No malignancy were during follow-up. No surgical procedure was performed on any patient.

DISCUSSION

MP is a disease of unknown etiology, characterized by a tumor-like mass consisting of chronic nonspecific inflammation, fat necrosis and fibrosis involving the mesenteric fat tissue (6,7). In 1924, mesenteric panniculitis was first described in the medical literature by Jura et al. In an autopsy study performed on more than 700 cases, MP was detected in 1% of the population (2,8). Although the incidence was observed more frequently in men in studies, it was observed more frequently in women in this study. (1,9).

Inflammatory disease of the mesentery is histologically characterized by a series of progressive changes. Initially, the mesentery is infiltrated by lipid-filled macrophages and is called mesenteric lipodystrophy.

As this condition progresses further and inflammation and fat necrosis are added, the acute and subacute form known as mesenteric panniculitis occurs. The chronic form, in which fibrosis and necrosis occur and shortening of the mesentery occurs, is known as retractile or sclerosing mesenteritis (10,11). In this study, clinical staging was not performed, all patients were evaluated under the diagnosis of mesenteric panniculitis.

Clinical findings are nonspecific and atypical. Abdominal discomfort, chronic abdominal pain, change in bowel habits, bleeding, intra-abdominal mass, fever, nausea, vomiting, chylous ascites and weight loss are the main clinical symptoms and complaints (10,12). The most frequently reported complaint in the literature is abdominal pain (3,13). In all of cases, the complaint of abdominal pain was at the forefront.

Symptoms may be progressive, or they may be self-limiting and regress in a short time. Mesenteric inflammation/fibrosis rarely causes shortening of the mesentery and compression of the mesenteric vessels, leading to the development of ascites, superior mesenteric vein thrombosis, mesenteric ischemia and ileus (14,15). In this study, no thrombosis, ischemia or ileus was observed in any patient.

Surgical intervention should be performed in serious complications of mesenteric panniculitis such as bowel obstruction or perforation; There are sources that argue that mild or asymptomatic patients can be followed up without treatment (16). There was no need for surgical intervention as no complications developed in the patients who were followed up.

Laboratory test results are usually normal. Studies have reported that there may be an increase in acute phase reactants (6). In this study, the leukocyte value was often within normal limits, and the CRP value was slightly high.

Diagnosis of mesenteric panniculitis is usually set by abdominal computed tomography and magnetic resonance imaging without the need for biopsy (5,17). ACT finding usually seen in mesenteric panniculitis; heterogeneous mass, localized to the mesentery or adjacent bowel loops, encapsulated, mostly on the left (2). All patients we followed were diagnosed with ACT (Figure 1, 2).

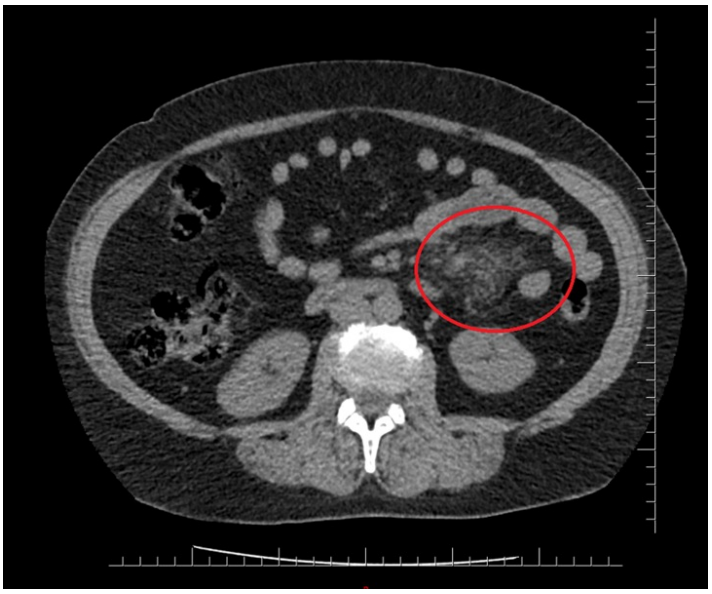

Figure 1. Tomography image of mesenteric panniculitis.

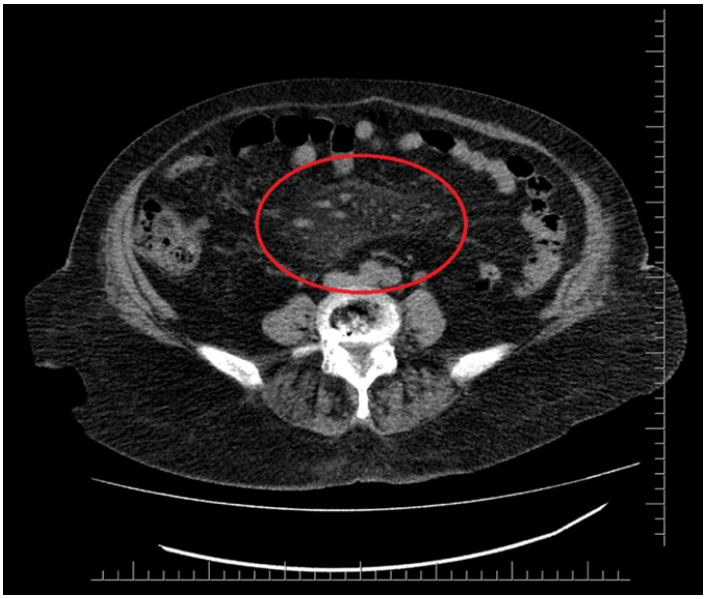

Figure 2. Tomography image of mesenteric panniculitis.

The course of this disease is mostly benign, it is self-limiting, and the inflammatory event regresses spontaneously (18). The treatments of the patients we followed varied, but none of them required surgical intervention. Recurrence was observed in 2 patients, and the complaints in these patients resolved with medical treatment. No malignancy was found during the follow-up of our patients.

There is no common approach to treatment. While many patients are followed up without treatment with conservative approaches, symptomatic patients who were treated with corticosteroids, azathioprine, cyclophosphamide, thalidomide and tamoxifen and were successful have been reported in the literature (1,13,19,20).

17 of our patients were given antibiotics and 15 were given anti-inflammatory drugs, and their complaints resolved during follow-up. Only 2 of the treated patients relapsed during follow-up. In the first treatment of relapsed patients, one was treated with antibiotics and the other with an anti-inflammatory drug. In the second treatment of relapsed patients, both were prescribed anti-inflammatory drugs.

CONCLUSION

In this study, contrary to the literature, MP was observed more frequently in women. No patient required a biopsy or invasive procedure for diagnosis. All patients were diagnosed with ACT. The leukocyte count was generally normal. No difference was observed in the follow-up of patients treated with only anti-inflammatory and those treated with antibiotics. We believe that the use of antibiotics in the treatment of mesenteric panniculitis is unnecessary and nonsteroidal anti-inflammatory drugs are effective in both pain control and regression of inflammation. However, more comprehensive studies with more patient groups and longer follow-up periods are needed.

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

Ethical permission was obtained from the Kahramanmaraş Sütcü İmam University, Medical Faculty Non-Invasive Clinical Research Ethics Committee for this study with date 17.06.2021 and number 313.

Authorship Contributions

Concept: GE, Design: GE, GD, Supervising: MU, Financing and equipment: GE, SA, Data collection and entry: GE, Analysis and interpretation: GE, SS, Literature search: GE, SA, SS, Writing: GE, GD, Critical review: MU

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1412206
Interdiscip Med J 2024;15(52):41-47

Factors associated with post-covid syndrome 3 months after covid-19 diagnosis

Hasan Açık[1], Gülen Açık[2]

[1] Istanbul Okan University, Faculty of Medicine, Department of Internal Medicine, Istanbul, Türkiye
[2] Istanbul Okan University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Istanbul, Türkiye

Abstract

Factors associated with post-covid syndrome 3 months after covid-19 diagnosis

Objective: Post-COVID Syndrome has been defined as a syndrome with chronic fatigue and psychiatric problems continue after COVID-19. In this study, it was aimed to evaluate patients' health-related quality of life standards 3 months after COVID-19 diagnosis.
Method: In this study, the psychosocial status and quality of life standards of patients, who were older than 18 years old and followed up due to COVID-19 in the outpatient clinic, ward, or intensive care unit of a university hospital, were assesed by the short form-36 scoring system.
Results: Of 67 patients, 57 were followed up and treated at home, nine were admitted to the ward, and one was admitted to the the intensive care unit. Short form-36 test scores of women patients, patients aged over 65, had at least one comorbid disease, and inpatient treatments during acute infection were found to be statistically significantly lower.
Conclusion: Gender, advanced age, presence of comorbidity, and history of hospitalization were determined as risk factors for Post-COVID Syndrome.
Keywords: COVID-19, Health-related quality of life, Long COVID, Post-acute COVID-19 syndrome, Symptom assessment.

INTRODUCTION

Even most of the patients experience symptoms such as fever, cough, and weakness in COVID-19, it may be fatal for some patients due to acute respiratory distress syndrome and multiple organ dysfunction syndrome (1). Post-COVID Syndrome (PCS) has been defined as a syndrome in which chronic physical and mental problems continue after COVID-19 (2). In many studies, it has been proven that symptoms observed in this syndrome can range from mild to severe enough to be unable to work and reducing the quality of life (QOL) (3,4). These symptoms include fatigue, headache, muscle and joint pain, shortness of breath, depression, sleep disorders, and anxiety disorders (5). In a review of eighteen studies, the most common symptom was found as fatigue in PCS. Depression was observed in 23% and anxiety in 22% of the patients. These symptoms were followed by memory and sleep problems (6). In a study conducted in Italy, in which patients were evaluated 7 weeks after discharge, it was observed that 97% of the patients had at least one symptom. The most common symptom was fatigue, and followed by shortness of breath and joint pain (1).

According to the literature, PCS is an extremely common problem. The mechanism behind PCS is not well understood, but it is assumed to be secondary to virus-specific pathophysiological changes, prolonged inflammatory response to acute infection, and sequelae of Post-Intensive Care Syndrome (3). We evaluated PCS with Short Form-36 (SF-36) questionnaire, which is widely acknowledged as the gold standard generic measure of health related QOL. SF-36 form is shown in Figure 1.

In this study, it was aimed to evaluate factors associated with PCS of patients, who were followed in the outpatient clinic, inpatient service, or intensive care unit of a university hospital 3 months after COVID-19 diagnosis.

Cite this article: Açık H, Açık G. Factors associated with post-covid syndrome 3 months after covid-19 diagnosis. Interdiscip Med J. 2024;15(52):41-47. https://doi.org/10.17944/interdiscip.1412206

Corresponding Author: Hasan Açık: Istanbul Okan University, Internal Medicine Department, Istanbul, Türkiye
Email: hasan.acik@hotmail.com
ORCID iD: 0000-0002-7247-8164

Received: Dec 30, 2023
Accepted: June 3, 2024

SF-36 Questionnaire

INSTRUCTIONS: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by circling the number that best represents your response.

1. In general, would you say your health is?

Excellent (1)	Very Good (2)	Good (3)	Fair (4)	Poor (5)

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago (1)	Somewhat better now than one year ago (2)	About the same as one year ago (3)	Somewhat worse now than one year ago (4)	Much worse now than one year ago (5)

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much: (circle one number on each line)

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
A. **Vigorous activities**, such as running, lifting heavy objects participating in strenuous sports	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C. Lifting or carrying groceries	1	2	3
D. Climbing **several** flights of stairs	1	2	3
E. Climbing **one** flight of stairs	1	2	3
F. Bending, kneeling, or stooping	1	2	3
G. Walking **more than a mile**	1	2	3
H. Walking **several hundred yards**	1	2	3
I. Walking **one hundred yards**	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Circle one number on each line)

	Yes	No
A. Cut down on the **amount of time** you spend on work or other activities		
B. **Accomplished less** than you would like		
C. Were limited in the **kind** of work or other activities		
D. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Circle one number on each line)

	Yes	No
A. Cut down on the **amount of time** you spend on work or other activities		
B. **Accomplished less** than you would like		
C. Did work or activities **less carefully than usual**		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbours, or groups? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

7. How much bodily pain have you had during the past 4 weeks? (Circle one)

None (1)	Very Mild (2)	Mild (3)	Moderate (4)	Severe (5)	Very Severe (6)

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time
A. did you feel full of life?	1	2	3	4	5
B. have you been very nervous?	1	2	3	4	5
C. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5
D. have you felt calm and peaceful?	1	2	3	4	5
E. did you have a lot of energy?	1	2	3	4	5
F. have you felt downhearted and depressed?	1	2	3	4	5
G. did you feel worn out?	1	2	3	4	5
H. have you been happy?	1	2	3	4	5
I. did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the Time (1)	Most of the Time (2)	Some of the Time (3)	A Little of the Time (4)	None of the Time (5)

11. How TRUE or FALSE is each of the following statements for you? (Circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

Figure 1: SF-36 Form

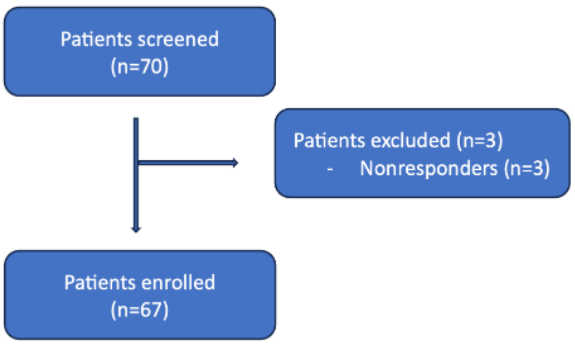

Figure 2:Flow chart

METHOD

Ethical permission was obtained from the Istanbul Okan University, Medical Faculty Ethics Committee for this study with date 20.20.2021 and number 20, and Helsinki Declaration rules were followed to conduct this study. Patients' consents were obtained via telephone. The study included cross-sectional retrospective data analyze and prospective questionnaire, which was conducted by applying the questionnaire via telephone to the patients 3 months after COVID-19 diagnosis, on November 2021. All patients enrolled in this study fullfilled the following criteria: being older than 18 years old and the disease confirmed by real time polymerase chain reaction (RT-PCR). Patients, who were under 18 years old, did not want to participate to the survey, died during this period, and diagnosis was not confirmed by RT-PCR were excluded from the study. Patients' age, gender, smoking status, comorbidities (diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and obesity, hospitalization status, and received COVID-19 treatments were recorded. Patients were contacted by telephone to evaluate with SF-36 questionnaire, which consists of eight main topics with a total of 36 questions, and provides the measurement of health related QOL. Eight main topics includes: physical functions (10 items), pain (2 items), limitations due to physical problems (4 items), limitations due to emotional problems (4 items), emotional well-being (5 items), social functions (2 items), fatigue (4 items), and general perception of health (5 items). Scores for each main topics range from 0 to 100, with a higher score defining a more favorable health state. First, we assessed factors associated with health related QOL. Second, we analyzed patients according to their ages, comorbidities, hospitalization statuses, and COVID-19 treatments.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were defined by the mean ± standard deviation, median (IQR: 25th and 75th percentiles) and categorical variables were defined by number and percent. Kolmogorov Smirnov and Shapiro Wilk tests were used for determination of normal distribution. For independent groups comparisons, we used Independent samples t test and One Way Analysis of Variance (post hoc: Tukey method) when parametric test assumptions were provided, Mann Whitney U test and Kruskal Wallis Variance Analysis (post hoc: Mann Whitney U test with Bonferroni Correction) were used when parametric test assumptions were not provided. Chi-square test was used to compare the categorical variables. To investigate the effects of independent variables on Quality of Life Total Scores (SF-36 Total Scores), we used univariate and multivariate linear regression models. Statistical significance was determined as $p<0,05$. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

We anaylzed the data of 70 patients retrospectively, and 67 patients accepted to participate the questionnaire (Figure 2). Median (IQR 25-75) age of all patients was 37 (30-47) years. Other demographic variables of patients presented in Table 1.

Table 1. Demographic variables of patients

Variables	Number	%
Gender		
Male	44	66
Smoking	19	28
Comorbidity		
DM	10	15
HT	6	9
CAD	3	5
COPD	2	3
Obesity	6	9
None	40	59
Hospitalization	9	13
COVID-19 treatment		
No treatment	11	16
Favipravir	48	72
Favipravir+steroid	8	12

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease

First, we analyzed the eight main factors' (physical function, pain, limitation due to physical problems, limitation due to emotional problems, emotional well-being, social function, fatigue, and general perception of health) association with age (young (18-40 years old)/ middle aged (41-64 years old)/ old (65 years and over)), gender (male/ female), smoking status (smoker/ nonsmoker), comorbidity (with/ without any comorbidity including DM, HT, CAD, COPD, and obesity), hospitalization (hospitalized/ nonhospitalized) and COVID-19 treatment (no treatment/ favipravir/ favipravir+steroid) (Table 2). There was a significant difference between SF-36 eight main topics and four variables including age, gender, comorbidity and hospitalization status. In addition, we analyzed SF-36 eight main topics association with these four variables.

We divided patients into three groups according to their ages; young (18-40 years old), middle (41-64 years old), and old (65 years old and over). Pain, limitation due to physical problems, emotional well-being, social function and general perception of health were significantly different between age groups (Table 3).

Table 2. Variables Associated with SF-36

Variables	Physical function	Pain	Limitation due to physical problems	Limitation due to emotional problems	Emotional well-being	Social function	Fatigue	General perception of health
Age	-0.301	-0.121	-0.353	-0.214	-0.073	-0.251	-0.192	-0.213
p values	0.013*	0.329	0.003*	0.082	0.559	0.04*	0.12	0.083
Gender	0.234	0.349	0.139	0.207	0.237	0.193	0.217	0.324
p values	0.056	0.004*	0.261	0.092	0.053	0.117	0.077	0.008*
Smoking	0.094	0.106	0.073	0.097	-0.014	0.168	-0.03	0.075
p values	0.45	0.393	0.555	0.434	0.913	0.174	0.811	0.549
Comorbidity	-0.482	-0.382	-0.42	-0.409	-0.419	-0.419	-0.42	-0.543
p values	0.0001*	0.001*	0.0001*	0.001*	0.0001*	0.0001*	0.0001*	0.0001*
Hospitalization	-0.564	-0.248	-0.52	-0.317	-0.293	-0.434	-0.258	-0.276
p values	0.0001*	0.043*	0.0001*	0.009*	0.016*	0.0001*	0.035*	0.024*
COVID-19 treatment	-0.162	0.075	-0.163	-0.033	0.109	-0.149	-0.043	-0.018
p values	0.189	0.546	0.188	0.792	0.381	0.227	0.73	0.883

All results represented with Standardized Beta Coefficient (p value); *p<0.05 statistically significant

Table 3. SF-36 Results according to age

Variables	18-40 years	41-64 years	≥ 65 years	P value			
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	Number	Med IQR(25-75)	
SF-36 scores							
Physical function	41	100 (87-100)	20	100 (90-100)	6	75 (17-100)	0.122 [kw]
Pain	41	100 (68-100)	20	100 (82-100)	6	55 (17-83)	0.031* [kw, c]
Limitation due to physical problems	41	100 (87-100)	20	100 (56-100)	6	50 (0-81)	0.009* [kw, b]
Limitation due to emotional problems	41	100 (67-100)	20	100 (42-100)	6	67 (25-100)	0.432 [kw]
Emotional well-being	41	64 (54-88)	20	86 (58-100)	6	50 (35-68)	0.05* [kw, c]
Social function	41	100 (75-100)	20	100 (100-100)	6	31 (22-66)	0.0001* [kw, b, c]
Fatigue	41	50 (35-75)	20	57 (26-84)	6	20 (7-45)	0.056[F]
General perception of health	41	75 (45-87)	20	75 (65-85)	6	37 (20-49)	0.019* [kw, b, c]

*p<0.05 statistically significant, [kw]: Kruskal Wallis Variance Analysis, [F]: One Way ANOVA, [a]: Significant difference between 18-40 years and 41-64 years groups, [b]:Significant difference between 18-40 years and ≥ 65 years groups; [c]:Significant difference between 41-64 years and ≥ 65 years groups

In gender, only pain (p=0.004) and general health perception (p=0.008) scores were lower in women. When the SF-36 scores were compared according the comorbidities, there was a statistically significant difference between patients without and with comorbidity. The mean SF-36 scores of patients with one or more comorbidities were found to be lower than patients without comorbidity in all eight main topics (Table 4). When we analyze comorbidities individually; patients with DM had significantly lower scores in limitation due to emotional problems (p=0.036) and fatigue (p=0.049). Patients with HT had significantly lower results in limitation due to physical problems (p=0.030), emotional well-being (p=0.035), social function (p=0.003), fatigue (p=0.025), and general perception of health(p=0.027). Patients with CAD had significantly lower results in pain (p=0.03), limitation due to physical problems (p=0.004), limitation due to emotional problems (p=0.038), emotional well-being (p=0.01), social function (p<0.001), and fatigue (p=0.017). Patients with COPD had significantly lower results in limitation due to physical problems (p=0.037) and general perception of health (p=0.006). There was no significant difference in SF-36 scores of patients with and without obesity.

Table 4. SF-36 results according to presence of comorbidity

Variables	With comorbidity	Without comorbidity	P value		
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	
SF-36 scores					
Physical function	27	75 (60-100)	20	100 (95-100)	0.001* [z]
Pain	27	73 (30-100)	20	100 (90-100)	0.001* [z]
Limitation due to physical problems	27	75 (18-100)	40	100 (87-100)	0.005* [z]
Limitation due to emotional problems	27	67 (33-100)	40	100 (67-100)	0.004* [z]
Emotional well-being	27	52 (43-68)	40	80 (60-100)	0.002* [z]
Social function	27	75 (34-100)	40	100 (100-100)	0.001* [z]
Fatigue	27	32 (19-51)	40	60 (37-82)	0.0001* [t]
General perception of health	27	42 (29-75)	40	80 (65-90)	0.0001* [z]

*p<0.05 statistically significant, [z]: Mann Whitney U Test, [t]: Independent Samples

Table 5. SF-36 results according to hospitalization

Variables	Hospitalized	Unhospitalized	P value		
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	
SF-36 scores					
Physical function	10	60 (30-95)	57	100 (94-100)	0.001* [z]
Pain	10	77 (16-100)	57	100 (76-100)	0.069 [z]
Limitation due to physical problems	10	25 (0-87)	57	100 (75-100)	0.001* [z]
Limitation due to emotional problems	10	67 (0-100)	57	100 (67-100)	0.077 [z]
Emotional well-being	10	48 (26-68)	57	72 (56-96)	0.016* [z]
Social function	10	50 (25-87)	57	100 (75-100)	0.001* [z]
Fatigue	10	20 (12-50)	57	50 (34-80)	0.035* [t]
General perception of health	10	40 (32-75)	57	75 (50-85)	0.022* [z]

*p<0.05 statistically significant, [z]: Mann Whitney U Test, [t]: Independent Samples

In the comparison of hospitalization, 57 patients (85%) were followed up and treated at home and 10 and 1 (1%) patient in the intensive care unit). Patients, who were treated at home did not receive any oxygen treatment; patients, who were treated at ward, received only oxygen support; and patients, who were treated in the ICU, received non-invasive mechanical ventilator. Except pain and limitation due to emotional problems, all six main topics were significantly different between hospitalized and unhopitalized patients (Table 5).

DISCUSSION

Age, gender, comorbidity, and hospitalization status of patients were found to be the factors associated with health related quality of life 3 months after COVID-19 diagnosis. In the current study, SF-36 scores of patients, who were aged 65 and over, were found to be lower in pain, limitation due to physical problems emotional well-being, and general perception of health. Our data are consistent with the literature review, which showed advanced age and presence of comorbidity increased the severity of both COVID-19 symptoms and PCS (3).

In this study, patients with comorbidity had lower scores in all eight main topics. Supporting this result, literature showed patients with comorbidity had worse COVID-19 symptoms and PCS (3) Contrary this result, Huang et al. (7) showed no significant association between comorbidity and PCS.

Our findings on DM agree with those reported by Su et al. (8), who found that diabetes poses a risk for PCS in patients who

have had COVID infection. In contrast, in a study conducted in Spain in which 144 diabetic patients were compared with healthy controls, it was found that diabetes was not a risk factor for PCS (9). In HT evaluation, a systematic review of 45 studies showed HT was a risk factor for PCS. It has been observed that one of the most common comorbid diseases in patients with PCS was hypertension. (10) Also, Tleyjeh et al. (11) found that patients diagnosed with hypertension were at a higher risk for PCS. However, a study in India showed that the most common comorbid disease among patients diagnosed with PCS was hypertension, but it was observed that hypertension was not a risk factor for PCS. (12). In COPD evaluation, likewise our results, Subramanian et al. (13) found that COPD was the most common risk factor for PCS. Our data differ from a study conducted in the USA showed that chronic lung diseases are not a risk factor for PCS (14). In CAD evaluation, a study, which compared healthy volunteers with people diagnosed with PCS, it has been determined that cardiovascular disease was not a risk factor for PCS. This situation can be explained by all the mechanisms that impair clinical outcomes in the acute phase of COVID-19, including obesity-related hyperinflammation, cytokine release, immune dysfunction, and comorbidities (16, 17). It was thought that the results of this study were inconsistent with the literature, because the number of obese patients (9%) was insufficient and 4 of 6 patients with obesity were under the age of 40.

Hospitalized patients had lower scores in physical function, limitation due to physical problem, emotional well-being, social function, fatigue, and general perception of health. Our data are consistent with Maestre-Muniz et al. (18), who showed hospitalized patients had more complaints than nonhospitalized patients 1 year after COVID-19 diagnosis.

Our findings on smoking agree with those reported by Huang et al. (7), who did not show any association between smoking and PCS. In the comparison of SF-36 scores between genders, women had significantly lower scores in pain and general health perception. In the literature review, the risk of ongoing symptoms after COVID-19 was found to be higher in women, which is consistent with this study (7, 19). Unlike Huang et al. (7), we observed no significant difference between COVID-19 treatments in SF-36 scores. They showed corticosteroid treatment during acute infection was a risk factor for ongoing fatigue and muscle weakness after 12 months. The reason for this is thought to be related with corticosteroid myopathy.

Limitations of the study

This study has some limitations. First, this study was a single-centered study with a small number of patients. Secondly, the inability to conduct face-to-face interviews with patients was also seen as a limitation. In addition, the decrease in the incidence of other viral infections due to COVID-19 caused us to form a control group.

CONCLUSION

Advanced age, gender, presence of comorbidity, and history of hospitalization were determined as risk factors for PCS. To evaluate other risk factors, more studies should be conducted on this subject. Identifying the risk factors is crucial in terms of predicting such a commonly encountered condition observed after COVID-19.

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

Ethical permission was obtained from the Istanbul Okan University, Medical Faculty Ethics Committee for this study with date 20.20.2021 and number 20, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: HA, GA, Design: HA, Supervising: HA, GA, Data collection and entry: HA, GA, Analysis and interpretation: HA, GA, Literature search: HA, Writing: HA, GA, Critical review: HA, GA

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1430781
Interdiscip Med J 2024;15(52):48-53

Retrospective evaluation of patients admitted to the emergency department due to drowning

Faruk Büyük[1], Melih Çamcı[2]

[1] Erciş Şehit Rıdvan Çevik State Hospital, Emergency Service, Van, Türkiye
[2] Department of Emergency Medicine, Ankara Bilkent City Hospital, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

Abstract

Retrospective evaluation of patients admitted to the emergency department due to drowning

Introduction: Drowning is a preventable process that can result in respiratory failure and death, and often occurs accidentally. In this study, it was aimed to evaluate the demographic characteristics and clinical course of the patients admitted to our emergency department in a district neighbouring a lake due to drowning.
Methods: Demographic characteristics, time of presentation, swimming ability, accident mechanism, predisposing factors, Glasgow coma scores (GCS), treatment, discharge, hospitalisation decisions, and mortality status of all patients admitted to our emergency department between January 2018 and January 2023 were recorded retrospectively from patient files and the digital automation system.
Results: Twenty (66.7%) patients were male and 10 (33.3%) were female; the patients wereaged between 6 months and 59 years, with a mean age of 14.06 years. An analysis of the site of incident revealed that 26 cases (86.6%) drowned in the lake and 4 cases (13.3%) drowned in a water canal. When we analysed the predisposing factors, it was found that one of the cases drowned after an accidental fall while walking on the rocks and one of the cases drowned after having chest pain and syncope. Among the cases with a GCS of 3, 1 of them died in the intensive care unit after 12 hours, 3 of them recovered with tracheostomy sequelae, and the remaining 14 cases died in the emergency department. Mortality was not observed in any of the 12 cases with a GCS of 14 or above. Fourteen cases died in the emergency department, 11 were referred to the intensive care unit, and 5 cases were discharged after emergency department follow-up. When we classified the patients according to Szpilman's clinical classification system, 8 cases were classified as Grade1, 4 cases as Grade 2, 16 cases as Grade 5, and 2 cases as Grade 6.
Conclusion: Raising awareness of families with children and increasing the necessary safety measures in water canals in summer months and in lakes is believed to reduce drowning-induced mortality. In addition to preventing drowning cases, providing the public with first aid training for drowning and healthcare professionals with appropriate assessment, intervention, and treatment algorithms may further reduce mortality.

Keywords: Drowning, Emergency Department, Retrospective Evaluation, Lakeside

INTRODUCTION

As per the recommendation of the World Health Organization (WHO), drowning was defined at the World Congress on Drowning, which was held in Amsterdam in 2002, as a process resulting from submersion/diving into a liquid medium, which progress when any liquid that prevents a person from breathing blocks that person's airway and breathing is impaired (1). Although it is a preventable public health problem as one of the causes of death resulting from unintentional injury with serious economic and health effects (2) while it is a type of accident causing a large number of deaths in our country (3), it is still an important but underrated universal public health problem (4).

Drowning is a completely preventable, acute, unexpected disaster that affects both adults and children. It is the third most common cause of accidental injuries, which is responsible for 7% of injury-related deaths (5). According to the data provided by WHO, drowning is one of the leading

Cite this article: Büyük F, Çamcı M. Retrospective evaluation of patients admitted to the emergency department due to drowning. Interdiscip Med J. 2024;15(52):48-53. https://doi.org/10.17944/interdiscip.1430781

Corresponding Author: Faruk Büyük, Erciş Şehit Rıdvan Çevik State Hospital Emergency Service, Van, Türkiye
Email: drfarukbuyuk@gmail.com
ORCID iD: 0000-0003-1456-7772

Received: Feb 2, 2024
Accepted: May 20, 2024

causes of death among children aged 5-14 years (6). Although the exact number is unknown, many new drowning cases occur each year in our country, particularly in summer months (7). In a domestic study, it was reported that 26.6% of drowning cases that took place between 2007 and 2011 occurred in sea, while the remainder occurred in natural or human-made fresh water environments such as rivers, lakes, and irrigation canals (3).

Factors such as duration of hypoxia, water temperature, timing and effectiveness of cardiopulmonary resuscitation, age of the victim, and the presence of comorbidities are important predictors of prognosis in drowning cases (8). In drowning cases, morbidity occurs due to anoxia and hypothermia, which culminate into metabolic acidosis as the common final pathway (9). Health outcomes of drowning survivors have longstanding effects, reaching up to severe injury to the brain or other organs (10). The remaining life of a drowning-survivor child with drowning-induced neurological deficit is deeply affected and long-term medical care may be needed. In a study it was reported that even 22% of children discharged without neurological sequela after a nonfatal drowning incident developed behavioral problems, communication problems, and learning disabilities at some point during their five-year follow-up (11).

Szpilman et al (12) developed the Szpilman clinical scoring, aiming to predict patient outcomes by evaluating them using vital signs and physical examination findings according to the scoring system at the accident scene.

In this study, it was aimed to assess the demographic features and clinical outcomes of drowning cases admitted to our district emergency department located near a lake.

METHOD

In this study, the information of male and female patients from all age groups who were admitted to a Secondary State Hospital's Emergency Service after 'drowning' between 01.01.2018 and 01.01.2023 was accessed from the hospital data automation system. The study included patients with adequate records regarding their age, sex, ability to swim, day of admission, month and season of admission, accident mechanism, predisposing factors, admission to the emergency department, Glasgow coma score (GCS), treatment-hospitalization-referral status, mortality status, and Szpilman classification at admission. GCS was divided into three subgroups according to the score obtained by the patients on admission to the emergency department in order to evaluate the mortality relationship significantly (13). At the same time, Szpilman's clinical classification was grouped into 2 subgroups to examine the relationship with mortality. Patients who did not meet the inclusion criteria and those whose medical information, especially vital signs could not be accessed were excluded.

Ethical approval

The design of the study was in line with the criteria of Helsinki Declaration. It was approved by Health Sciences University, Van Training and Research Hospital Clinical Studies Ethics Committee Chairmanship (Date and Decision

Statistical analysis

Statistical analyses were carried out with SPSS (IBM SPSS Statistics v.27) statistical software package. Frequency tables and descriptive statistics were used to interpret the findings. Categorical variables were expressed as % (percentage). Comparison of categorical variables was carried out using Chi-square test. Satistical significance was set at $p<0.05$.

RESULTS

A total of 30 patients were enrolled. The distribution of their demographic characteristics was shown on Table 1. Examining the age and gender distribution of the cases reveals that most victims are male (n = 20, 66.7%) and the 2–12 years age group was predominant (n=15, 50%) (Table 1).

Table 1. Distribution of the demographic characteristics of the patients

Variable (N=30)	n	%
Sex		
Female	10	33,3
Male	20	66,7
Age Distribution		
0-2	5	16,7
2-12	15	50
12-18	3	10
18-65	5	16,7
Over 65	2	6,7

The patient distribution with respect to ability to swim, temporal distribution of the cases, accident mechanism, and predisposing factors were shown on Table 2. A few patients (n=9, 30%) admitted to the emergency department due to drowning were able to swim, while the majority (n=9, 70%) were unable to swim. An analysis of the the temporal distribution of the cases revealed that 19 (63.3%) patients were admitted on weekdays and 11 (36.7%) presented on weekends. It was also observed that drowning cases (n=22, 73.3%) occurred predominantly in the summer months. When the predisposing factors were closely examined, drowning in a lake was found to be common (n=24, 80%).

The data on the vital signs of patients who were admitted to the emergency department due to drowning were shown on Table 3. According to Glasgow Coma Scale, the patients were grouped into three groups. There were more cases with a GCS

Table 2. Distribution of the cases by the ability to swim, temporal distribution of admissions, accident mechanism, and predisposing factors

Variable (N=30)	n	%
Ability to swim		
Present	9	30
Absent	21	70
Daily distribution of cases		
Weekdays	19	63.3
Weekend	11	36.7
Monthly Distribution of cases		
August	7	23.3
October	1	3.3
September	2	6.7
June	8	26.7
May	3	10.0
July	9	30.0
Seasonal distribution of cases		
Spring	5	16.7
Fall	3	10.0
Summer	22	73.3
Accident mechanism		
Acute Coronary Syndrome	1	3.3
Accident	29	96.7
Predisposing Factors		
Acute Coronary Syndrome in Lake	1	3.3
Drowning in Lake	24	80.0
Falling off the cliffs	1	3.3
Drowning in irrigation canal	3	10,.0
Falling into irrigation canal	1	3.3

between 3-5 (n=18, 60%) than those with a GCS between 10-15 (n=12, 40%). Of the patients presented to the emergency department, 13 patients died despite interventions, 11 were referred to the intensive care unit, and 5 were discharged. Fifteen out of a total of 30 patients died. Among the 15 survivors, 12 recovered without sequela. A mortality analysis by age revealed that those who died were mostly older than 12 years of age. According to the Szpilman classification, 12 patients had a score of 1-3, and 18 patients had a score of 3-6. Chi-square test of independence was performed to examine the relationship between mortality and sex, ability to swim, GCS, and Szpilman classification, the results of which were shown on Table 4. Mortality and sex were not significantly correlated ($p>0.05$). However, mortality and the ability to swim were significantly correlated ($p=0.014$). Death occurred

Table 3. Glasgow Coma Score, prognosis, mortality status, and Szpilman classification of the patients

Variable (N=30)	n	%
Glasgow Coma Score		
3-5	18	60.0
5-10	0	0
10-15	12	40.0
Treatment-hospitalization -referral status		
Deceased at emergency department	13	43.3
Admission to adult ICU	1	3.3
Deceased at scene	1	3.3
Referred to pediatric ICU	10	33.3
Discharge	5	16.7
Mortality status		
Survived	15	50
Deceased	15	50
Mortality status Detailed		
Recovery without sequela	12	40
Recovery with sequela (Tracheostomized)	3	10
Deceased	15	50
Szpilman classification		
1	8	26.7
2	4	13.3
3	0	0
4	0	0
5	16	53.3
6	2	6.7
Szpilman classification2		
1-3	12	40
3-6	18	60

in 88.9% of patients who could swim and 33.3% of those who could not. Mortality and Glasgow Coma Score were significantly correlated ($p<0.01$). Whereas 83.3% of patients with a GCS of 3-5 died, none of those with a GCS of 10-15 died. This suggests that mortality rate increased in patients with a lower GCS and it decreased in those with a high GCS. Mortality and Szpilman classification were also significantly correlated ($p<0.01$). No death occurred for a Szpilman score of 1-3 whereas 83.3% of patients with a Szpilman score of 3-6 died.

On Table 5, sex, ability to swim, GCS, and Szpilman classification of the surviving cases as well as the deceased were examined in detail.

Table 4. Examination of the correlations between mortality and sex, ability to swim, Glasgow Coma Score, and Szpilman classification

Variable (N=30)	Mortality				Statistical analysis* Likelihood
	No		Yes		
	n	%	n	%	
Sex					
Female	5	50	5	50	χ^2=0
Male	10	50	10	50	**p=1**
Ability to swim					
Present	1	11.1	8	88.9	χ^2=7.778
Absent	14	66.7	7	33.3	**p=0.014**
Glasgow Coma Score					
3-5	3	16.7	15	83.3	χ^2=16.806
10-15	12	100	0	0	**p<0.001**
Szpilman classification					
1-3	12	100	0	0	χ^2=16.806
3-6	3	16.7	15	83.3	**p<0.001**

Table 5. Examination of the correlations between mortality and sex, ability to swim, Glasgow Coma Score, and Szpilman classification

Variable (N=30)	Mortality						Statistical analysis* Likelihood
	Recovery without sequela		Recovery with sequela		Deceased		
	n	%	n	%	n	%	
Sex							
Female	4	40	1	10	5	50	χ^2=0.257
Male	8	40	2	10	10	50	**p=1**
Ability to swim							
Present	1	11.1	0	0	8	88.9	χ^2=6.999
Absent	11	52.4	3	14.3	7	33.3	**p=0.022**
Glasgow Coma Score							
3-5	0	0	3	16.7	15	83.3	χ^2=32.839
10-15	12	100	0	0	0	0	**p<0.001**
Szpilman classification							
1-3	12	100	0	0	0	0	χ^2=32.839
3-6	0	0	3	16.7	15	83.3	**p<0.001**

DISCUSSION

Drowning is one of the common and preventable causes of death, both around the world and in our country. Approximately 1000 people die as a result of drowning each year in our country (3,4). In this study, it was aimed to evaluate both the demographic features and the clinical outcomes of patients who presented to our emergency department due to drowning, and to raise the awareness of the regional people of drowning; it demonstrated that a great majority (66.7%) of drowning accidents affected males. Another study from Turkey reported that 84% of drowning victims were men (3). Two international studies reported from China and Iran also found similar results, reporting a greater percentage of men (13,14). This shows that men suffer more drowning accidents. This may be attributed to men showing a more dangerous behavior pattern in water, spending more time in water than women, and having more desire to swim alone, whereas women prefer to swim in safer environments (such as swimming in places with lifeguards nearby, swimming close to the shore) than men.

In this study, it was determined that drowning cases were mostly 2-12 years old. In a study conducted on drowning cases in Diyarbakir province, deaths mostly occurred in the 0-10 years age group, followed by 11-20 and 21-30 years age groups (15). In a study conducted by Dia L et al (13) from China, it was reported that the age groups with the highest frequency of drowning cases were found to be 5-9 and 10-14 years age groups. Morgenstern et al (16) from the USA found that for each adult person that is killed by drowning, 3.1 children are killed by drowning. A study reported from the United Kingdom revealed that 81% of all hospitalized drowning cases were 0-4 years old (17). In this study, it was determined that the age group highlighted is also similar. Accumulation of drowning cases in the childhood and young adulthood years can be explained by a lower ability to perceive danger and having a greater tendency to perform dangerous acts in these years of life. Adolescent children, particularly boys, are at increased risk of drowning due to their tendency of participating in more risky water activities and showing off their closed ones and families with their swimming abilities.

It was found that 70% of patients who presented to our emergency department after a drowning accident were unable to swim. No matter what the onset is, the ability to swim and drowning were not directly correlated. Even people who are very good at swimming may drown (4). The higher percentage of patients that were unable to swim can be attributed to the larger proportion of children in our group.

An analysis of the temporal distribution of the admitted cases showed that 63.3% of them presented to the emergency department on weekdays, which was believed to be due to a smaller number of people swimming during working hours, which may lead to underdetermining of drowning cases. A closer look at the seasonal distribution of the cases revealed that 73.3% of the cases occurred in summer. Studies published from our country have also reported that drowning cases frequently occurred in summer (18,19), paralleling to this study.

A retrospective South African study found that drowning accidents were more frequent in public holidays and summer (20). A study spanning four years which examined drowning cases by season and month found that the cases mostly occurred in summer months and also hot regions (21). Similar findings were obtained in another study reported from China (13). We believe that the cases mostly occurred in summer because this season is traditionally the holiday season, and people commonly prefer swimming for cooling off and having fun. Considering the geographical and socioeconomic status of our district located nearby a lake, we think that residents of the area prefer the lake for entertainment and holidays instead of traveling distant holiday resorts.

In this study, it was found that our results were inconclusive regarding predisposing factors and accident mechanisms, largely because of limited data due to the inability to obtain sufficient data from retrospectively scanned records.

According to the Glasgow Coma Score measured at the time of emergency department admission, the patients were grouped into two groups. There were 18 (60%) patients with a score of 0-5, and 12 (40%) patients with a score of 10-15. Thirteen patients who presented to the emergency department died despite interventions, 11 were sent to intensive care unit, and 5 were discharged. A total of 15 patients out of 30 died. Recovery without any sequela were observed in 12 of 15 patients that survived the incident. A domestic study concluded that, among those with a GCS above 14 at the time of hospital admission, the prognosis was good and no death occurred whereas those with a GCS of 4 or lower had a worse prognosis (22). Ballesteros et al (21) found that a GCS of 5 or lower was directly correlated to mortality among 43 cases followed at an intensive care unit after successful cardiopulmonary resuscitation. In another study conducted in Germany, a GCS below 3-5 was one of the poor prognostic indicators in drowning cases (23). In this study, it was found that, in line with the literature data, a GCS of 5 or lower was decisive in predicting a worse prognosis. It was also found that 83.3% of patients with a GCS of 3-5 died whereas none of those with a GCS of 10-15 died. These data indicate that the mortality rate increased in those with a low GCS while it decreased in those with a higher GCS.

According to the Szpilman classification in which patients were classified by the clinical presentation at admission, 12 patients had of score of 1-3 and 18 patients had a score of 3-6. Söyüncü et al (22) reported that all patients with a Grade 6 Szpilman score. In a study published in the Korean Journal of Pediatrics, it was found that Szpilman clinical scoring system might be as useful as consciousness level in predicting mortality according to clinical parameters at admission (24). In this study, it was also found that there was a significant correlation between mortality and Szpilman classification ($p<0.001$). According to the Szpilman classification, no patient with a score of 1-3 died whereas 83.3% of patients having a score of 3-6 died.

Limitations of the study

In this study dealt with parameters with low statistical significance owing to its small-scale and retrospective design. Since the scores of the scoring systems were calculated from the recorded data, we believe that prospective studies would be more beneficial for studying the subject more comprehensively. In addition, drowning cases occurring in sea were excluded by the study since we only reviewed drowning cases that occurred in lakes or irrigation canals.

CONCLUSION

Drowning, which is one of the preventable accidents, is a significant public health issue. Although children are particularly at risk, necessary safety measures and trainings should be specifically planned for different age groups. Clinical signs at emergency department admission and Szpilman classification are helpful in predicting the prognosis and mortality risk of drowning victims. It is important that citizens living in settlements located geographically near to lakes are trained about and made aware of drowning, and that healthcare staff working in hospitals' emergency services have a good grip of the current literature and practical applications on this subject.

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

Ethical permission was obtained from the Health Sciences University Van Training and Research Hospital Clinical Studies Ethics Committee Chairmanship approved the study (Date and Decision No. 04. 10. 2023, 2023/ 21-05) and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: FB, MÇ, Design: FB, MÇ, Supervising: FB, MÇ, Financing and equipment: FB, MÇ, Data collection and entry: FB, MÇ, Analysis and interpretation: FB, MÇ, Literature search: FB, MÇ Writing: FB, MÇ, Critical review: FB, MÇ

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1432324
Interdiscip Med J 2024;15(52):54-59

Clinical significance of mean platelet volume, platelet distribution width, and neutrophil-lymphocyte ratio in children with familial Mediterranean fever

Gül Trabzon[1], Müferet Ergüven[2], Didem Kızmaz İsançlı[3], Emine Olcay Yasa[4]

[1] Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Pediatric Endocrinology, Hatay, Türkiye
[2] Düzce University Faculty of Medicine, Department of Pediatric Rheumatology, Düzce, Türkiye
[3] Okmeydanı Training and Research Hospital, Pediatric Infection Clinic , Istanbul, Türkiye

Abstract

Clinical significance of mean platelet volume, platelet distribution width, and neutrophil-lymphocyte ratio in children with familial Mediterranean fever

Objective: Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent fever and polyserositis. Studies conducted in recent years emphasize the importance of platelet parameters in chronic diseases. This study examined changes in attack and attack-free periods in children with FMF, focusing on Mean Platelet Volume (MPV), an indicator of disease severity.
Method: 150 FMF patients (90 girls, 60 boys) and 50 healthy individuals (29 men, 21 women) were included in the study. Data were analyzed according to colchicine treatment, attack, and attack-free periods. The severity of the disease was classified as mild, moderate, and severe.
Results: MPV levels of patients with FMF were higher than the healthy group. In particular, MPV levels decreased significantly during attacks, with a more pronounced decrease in severe cases.
Conclusion: As a result, MPV measurement is a cost-effective and rapid method that can support the evaluation of disease severity and attack periods in FMF patients.
Keywords: Familial Mediterranean Fever, mean platelet volume, Neutrophil/Lymphocyte Ratio, M694V mutation

INTRODUCTION

Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever and polyserositis, particularly affecting ethnic groups around the Mediterranean, i.e., individuals of Sephardic Jewish, Armenian, Arab, and Turkish descent (1). The diagnosis of FMF is established based on the Tel-Hashomer criteria. With the detection of the gene causing the disease in 1997, mutational analysis became a viable auxiliary diagnostic method in suspicious cases (2,3). Although the etiopathogenesis of the disease has not been completely elucidated, it is thought that the innate immune system plays a significant role. A widely accepted hypothesis is that the pyrin/marenostrin protein encoded by the MEFV gene fails to suppress neutrophil-mediated inflammation, which results in a clinical picture of short-lived inflammatory episodes and periodic fever (3).

Typically, no clinical complaint occurs during attack-free periods in FMF. However, studies have indicated high cytokine levels in these periods, possibly linked to subclinical inflammation. Systemic inflammation leads to diminished anticoagulant and fibrinolytic activity after the secretion of coagulation precursors, predisposing the patient to thrombosis (4,5). Clinical and subclinical inflammation in FMF is known to cause endothelial dysfunction and thereby trigger the coagulation cascade. In addition, extracellular matrix proteins fibronectin and thrombospondin levels are shown to increase during FMF attacks (6,7).

Cite this article: Trabzon G, Ergüven M, İsançlı DK, Yasa EO. Clinical Significance of mean platelet volume, platelet distribution width, and neutrophil-lymphocyte ratio in children with familial Mediterranean fever. Interdiscip Med J. 2024;15(52):54-59. https://doi.org/10.17944/interdiscip.1432324

Corresponding Author: Gül Trabzon, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Pediatric Endocrinology, Hatay, Türkiye
Email: gldirekk@gmail.com **ORCID iD:** 0000-0002-9262-5678

Received: Feb 13, 2024
Accepted: May 20, 2024

Accurate measurement of mean platelet volume (MPV) by electronic cell counters has made MPV a commonly assessed parameter in clinical studies and practice. In increased thrombopoiesis, high MPV has been reported due to high levels of circulating young platelets. Large platelets also called "stress" platelets, contain higher rates of dense granules and exhibit elevated biochemical, functional, and metabolic activity. MPV increases in accelerated peripheral platelet destruction and decreases in impaired platelet production. Higher MPV level is associated with elevated growth of megakaryocytes due to thrombopoietin response. Several clinical conditions linked to inflammatory responses demonstrate elevated MPV levels, although in certain cases, MPV may exhibit a decrease (7,8,9).

Platelet distribution width (PDW) is another marker of platelet activation linked with inflammation and atherothrombotic events. Various studies have reported that PDW is a more specific indicator of platelet activation than MPV . By established hematological protocols, PDW is derived in conjunction with other platelet volume indices (mean platelet volume, MPV; plateletcrit, PCT), serving as a parameter calculated mathematically from platelet volume measurement and the standard deviation of volume distribution among the platelet population (10,11). Recent studies have suggested that neutrophil-lymphocyte ratio (NLR) can also be used as a subclinical inflammation marker in FMF, but further evidence is necessary to establish the reliability of the parameter (12).

The parameters MPV (mean platelet volume), PDW(platelet distribution width), and NLR (neutrophil-to-lymphocyte ratio) may be potential utility as indicators of systemic inflammation (12-15).

This study aims to investigate the clinical importance of hematological parameters - especially mean platelet volume (MPV), platelet distribution width (PDW), and neutrophil-lymphocyte ratio (NLR) - in children with Familial Mediterranean Fever (FMF) disease. FMF is an autosomal inherited inflammatory disease characterized by recurrent fever attacks, peritonitis, pleuritis, and arthritis. However, there are limited studies on hematological markers of the disease.

This study aims to determine the clinical value of these markers in the pediatric population of FMF. The study's focus specifically on hematological parameters such as MPV, PDW, and NLR points to the existence of simple and widely accessible markers that may help in the early identification of inflammation-related complications of FMF. The results of this study may help us better understand the clinical use of hematological parameters in children diagnosed with FMF and develop more effective strategies for the management of the disease.

The present study investigated the correlation between disease severity and changes in MPV, PDW, and NLR levels during attacks and attack-free periods in children with FMF. We aimed to evaluate the clinical utility of these parameters as inflammation markers in FMF cases. This study aims to investigate the clinical importance of hematological parameters - especially mean platelet volume (MPV), platelet distribution width (PDW), and neutrophil-lymphocyte ratio (NLR) - in children with Familial Mediterranean Fever (FMF) disease. However, there are limited studies on hematological markers of the disease. This study aims to determine the clinical value of these markers in the pediatric population of FMF.

METHOD

In this study, 150 patients who were followed up in Medeniyet University Göztepe Training and Research Hospital Pediatric Rheumatology Outpatient Clinic between 2009-2014 and diagnosed with FMF according to Tel-Hashomer criteria were retrospectively analyzed. Medeniyet University Göztepe Training and Research Hospital ethics committee approval was obtained on 23.09.2014 with the decision number 2014/0147. Patients with concomitant chronic diseases were excluded from the study. The patient group was examined in terms of demographic characteristics, symptoms, Pras severity score, development of amyloidosis, and genetic test results. Disease scoring(Pras severity score) was based on the age of onset, frequency, and severity of joint involvement, presence of erysipelas-like erythema, and colchicine dose required for symptom control; as a result, disease severity was classified as severe, moderate, or mild (15). Laboratory parameters, including hemoglobin, white blood cell (WBC) count, platelet count, MPV, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and proteinuria, were obtained during attacks and attack-free periods. Complete blood counts were analyzed with a daily-calibrated hemocytometer (Abbott Cell-Dyn 3700 System, Abbott Diagnostics, Santa Clara, CA, USA) using samples anticoagulated with K3EDTA. The control group consisted of 50 individuals who presented to the Ministry of Health Göztepe Training and Research Hospital Pediatrics Outpatient Clinic for routine control and had no complaints or chronic diseases. The healthy controls were compared with the patient group regarding hemogram parameters. The principles of the Declaration of Helsinki were complied with when the study was conducted.

Statistical analysis

The conformity of continuous variables to the normal distribution was evaluated with the Shapiro-Wilk test. Levene's

test analyzed the homogeneity of variance. In comparisons, a t-test was used and shown with 't' for comparing the values during the attack and attack-free periods within the dependent groups in the same patient group. When the three groups including the control group were compared, a one-way ANOVA test was used for comparison and denoted by a. The results were presented as mean±SD. Two-way tables were evaluated with Pearson's chi-squared and Fisher's exact tests. All analyses were performed using the SPSS software package (SPSS version 16.0, SPSS Inc., Chicago, IL, USA). Results were presented in numbers (n) and percentages (%). A p-value of <0.05 was considered statistically significant.

Table 1. Distribution of MEFV mutations in patients

Mutation	Mutation-positive patients (n: 150)	Percentage
M694V/ M694V	48	29.8%
M694V/N	23	14.3%
E148Q/N	12	7.5%
M694V/M680I	10	6.2%
M680I/N	4	2.5%
M694V/E148Q	4	2.5%
M694V/V726A	3	1.9%
M680I/680I	3	1.9%
M694I/V726A	3	1.9%
M694V/R761H	2	1.2%
V726A/N	2	1.2%
M694V/P369S/ E148Q	1	0.6%
M680I/V726A	1	0.6%
M694V/M694I/ E148Q	1	0.6%
E148Q/P369S	1	0.6%

Note: Two different mutations separated by "/" indicates a compound heterozygous mutation, single mutation/N indicates a single heterozygous mutation, and the same mutation written twice indicates a homozygous mutation.

RESULTS

The patients' mean age at diagnosis was 8.1±4.0 years, and the mean attack frequency was 1.6 attacks per month. Twenty patients had mild FMF, 113 had moderate FMF, and 17 had severe FMF. All patients were evaluated regarding MEFV gene mutations (Table 1). The most frequent mutation was the M694V homozygous mutation in 29.8% of patients.

The patients' hemoglobin, WBC count, MPV, platelet count, PDW, NLR, CRP, and ESR values were studied during attacks and attack-free periods (Table 2). Hemoglobin and MPV levels were significantly lower during attacks, whereas no significant difference was observed between attacks and attack-free periods regarding platelet count. During attacks, the WBC count, CRP, ESR, PDW, and NLR levels were significantly higher.

Table 2. Comparison of patient laboratory parameters between attacks and attack-free periods

	Attack	Attack-Free Period	Control	P-Value
Hemoglobin (g/dL)	11.93±1.95	12.42±1.62	12.75±1.30	<0.001
WBC count (/mcL)	10144±2042	9215±1855	8777±2679	<0.001
MPV (fl)	6.95±0.20	7.47±0.36	7.62±1.32	<0.001
Platelet count (/mcL)	372(K)±11(K)	344(K)±62(K)	307(bin)±66(bin)	0.157
AST (IU/L)	28.63±12.44	29.45±9.85	--	<0.001
ALT (IU/L)	15.44±7.36	18.78±6.55	--	<0.001
BUN (mg/dL)	12.46±3.57	11.68±1.34	--	<0.001
Creatinine (mg/dL)	0.72±0.20	0.85±0.31	--	<0.001
PDW	17.6±4.0	15.5±2.20	17,20±0.87	<0.001
NLR	2.57±0.37	1.16±0.18	1,44±0,79	<0.001
CRP (mg/L)	37.55±24.48	0.25±0.08	--	<0.001
ESR (mm/hour)	28.17±7.50	14.52±5.40	--	<0.001

The patients MPV levels during attacks were significantly lower than those in the attack-free periods, and their MPV levels significantly decreased as disease severity increased. A significant negative correlation was observed between the patients' MPV levels during attacks and attack-free periods (p: 0.002) (Table 3).

Table 3. Relationship between disease severity and attack and attack-free MPV levels

MPV Levels	Disease severity		
	Mild	Moderate	Severe
Attack-free MPV (fL)	8.93±1.15	8.72±0.84	8.49±0.98
Attack MPV (fL)	8.81±1.10	8.55±0.80	8.21±0.80

Table 4. Relationship between disease severity and attack and attack-free PDW levels

Pdw Levels	Disease severity		
	Mild	Moderate	Severe
Attack-Free Pdw	15.74±0.95	16.02±1.02	16.15±1.23
Attack Pdw	18.23±2.13	18.45±2.50	18.62±2.24

Table 5. Relationship between disease severity and attack and attack-free NLR levels

Neutrophil-Lymphocyte Ratio	DISEASE SEVERITY		
	MILD	MODERATE	SEVERE
Attack-free NLR	1.37±0.42	1.45±1.10	1.44±0.80
Attack NLR	2.04±1.17	2.89±3.18	4.75±4.00

An evaluation of the relationship between disease severity and PDW levels during attacks and attack-free periods revealed that PDW levels significantly increased as disease severity increased ($p<0.001$) (Table 4). A significant positive correlation was observed between the PDW levels during attacks and attack-free periods (p: 0.003) (Table 4).

An evaluation of the relationship between disease severity and NLR levels during attacks and attack-free periods revealed that NLR levels significantly increased as disease severity increased (p-<0.001) (Table 5). Although a positive correlation was observed between NLR levels during attacks and attack-free periods, no statistical significance was seen. (p: 0.073) (Table 5).

DISCUSSION

Studies have shown that cytokine levels remain high and subclinical inflammation continues in the attack-free periods of FMF, suggesting a possible effect on patients' predisposition to thrombosis (4,16). MPV has been widely investigated as a marker of platelet activation in FMF patients (17). A study by Çoban et al. on adult patients reported higher MPV levels in attack-free FMF patients than in healthy controls (18). The findings of the present study are similar. It was thought the increased platelet production could explain high MPV levels in FMF patients having chronic low-grade inflammation, the elevated circulating platelet count, and the migration of young, reactive, and more giant platelets toward the site of inflammation. Contrary to the study conducted by Yorulmaz et al., in this study, when we compared FMF patients among themselves, it was seen that MPV levels during the attack were significantly lower than in the attack-free period (9). This can be attributed to the inflammatory destruction of more giant platelets migrating to the site of inflammation. It is expected that MPV levels will decrease when giant platelets disappear (19). As disease severity increases, MPV levels decrease. As the severity of the disease increases, the destruction of giant platelets increases and the MPV levels decrease further, which may also explain this result. In addition, among our FMF patients, PDW levels during attacks were significantly higher than those in the attack-free periods, and a significant positive correlation was observed between disease severity and PDW levels. In a study evaluating PDW and MPV, Uluca et al. indicated that MPV and PDW levels were unaffected in childhood FMF. The authors attributed this to the suppression of inflammation due to colchicine therapy (20). FMF patients in this study were also on colchicine therapy, but our results were different. In addition, NLR levels during attacks were significantly higher than those in attack-free periods, which was possibly linked to increased neutrophil counts due to inflammation.

Limitations of the study

The study acknowledges certain limitations that warrant consideration when interpreting the findings. Firstly, the influence of colchicine therapy on laboratory parameters and disease severity in Familial Mediterranean Fever (FMF) patients, a crucial aspect of the management, is not comprehensively explored in this research. The impact of colchicine, a standard treatment for FMF, on the observed results remains a potential factor that requires further investigation. Secondly, the study primarily focuses on MEFV gene mutations, offering valuable insights into the genetic aspect of FMF. However, it's important to note that genetic diversity can vary significantly among different populations. The predominantly narrow focus on MEFV mutations may limit the generalizability of the findings to populations with diverse genetic backgrounds, and caution is needed when applying these results to broader demographic groups

CONCLUSION

This is one of the few articles investigating the relationship between hematological parameters and inflammation in FMF attack, attack-free period, and control groups, and is important in terms of elucidating these periods. In this study, MPV levels were higher among FMF patients than healthy controls and dropped during attacks from levels in attack-free periods and decreased further as disease severity increased. These results suggest that MPV could be used as a negative marker for identifying attack phases in FMF patients. Additionally, increases in PDW and NLR levels were observed with escalating disease severity, highlighting their potential as indicators of inflammation severity.

Our study demonstrates that hematological parameters can serve as useful tools in the clinical management of FMF; however, further research is needed to fully understand the impact of colchicine treatment on these parameters. Future studies should expand upon our findings and include patients from diverse ethnic backgrounds to assess the applicability of our results to a broader population.

The integration of regular monitoring of hematological parameters, especially during attack periods and across different severity levels, could enhance clinical practices in FMF management. Continued research into the underlying mechanisms of these findings and their implications for disease management is essential. To conclude, MPV, PDW, and NLR measurements offer an easy, inexpensive, and rapid method to detect attacks and determine disease severity in FMF patients. Future studies will firmly establish the efficacy of MPV, PDW, and NLR as markers in FMF assessment.

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

Ethical permission was obtained from the İstanbul Medeniyet University, Medical Faculty Clinical Ethics Committee for this study with date 23.09.2014 and number 2014/0147 and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: GT, ME, Design: GT, ME, Supervising: ME, EOY, Financing and equipment: GT, DKI, Data collection and entry: GT, DKI, Analysis and interpretation: GT, ME, EOY, Literature search: GT, DKI, Writing: GT, Critical review: ME, EOY.

Thesis

This study was prepared by rearrangement of the specialty thesis by Gül Trabzon entitled as “Clinical Significance of Mean Platelet Volume, Platelet Distribution Width, and Neutrophil-Lymphocyte Ratio in Children with Familial Mediterranean Fever”.

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1444084
Interdiscip Med J 2024;15(52):60-66

Comparison of effectiveness indicators before and during the COVID-19 pandemic in a university hospital

Mehmet Erdem[1], Bircan Kara[2], Sibel Armağan Karadeniz[1]

[1] Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Public Health, Hatay, Türkiye
[2] Hatay Mustafa Kemal University Hospital, Hatay, Türkiye

Abstract

Comparison of effectiveness indicators before and during the COVID-19 pandemic in a university hospital

Objective: Our aim in this study is to reveal to what extent hospital efficiency indicators changed in a University Hospital between the period before the Covid 19 pandemic (2018-2019) and the period when the pandemic started and continued (2020-2021).
Method: The study planned as a retrospective and descriptive type, data belongs to a 4-year period (2018-2021). The number of personnel for the years examined in the study, the number of applications to the outpatient clinic and emergency department calculated monthly and the number of deceased patients. Bed occupancy rate, inpatient rate, average patient stay days, bed turnover rate and bed turnover interval were used as hospital bed utilization efficiency indicators.
Result: Among all years, April 2020 had the lowest number of emergency applications (n=1287) and total number of outpatient clinic applications (n=7530). The year with the highest bed occupancy rate was 2020 with 77.2±6.7. The highest inpatient rate was in 2020 with 6.7±2.1, the highest average day of stay was in 2021 with 10.8±2.2, the highest bed turnover rate was in 2018 and 2019 with 4.7±0.3 and the highest bed turnover interval was observed in 2021 with 5.2±2.2. April 2020 was the month with the highest inpatient rate at 11.8% and the highest bed turnover interval at 16.8.
Conclusion: The number of patients applying to emergency departments and outpatient clinics decreased, the inpatient rate increased, the bed turnover rate decreased, the bed turnover interval extended and the average day of stay increased during the pandemic period.
Keywords: Pandemic, COVID-19, Bed Occupancy Rate, Bed Turnover Rate

INTRODUCTION

In December 2019, cases of pneumonia of unknown cause were first reported in Wuhan, China. The pathogen called severe acute respiratory syndrome coronavirus 2 was isolated from the lower respiratory tract of infected patients, and the resulting disease was named COVID-19 (1). Restrictions began to be imposed in Turkey as of March 16, 2020, to prevent the spread of the virus. A full-time curfew started from Thursday, April 29, 2021 until Monday, May 17, 2021. First, schools and all public places were closed. Flexible working hours were introduced for public service employees, flexible working hours were introduced in hospital outpatient clinics, and the number of outpatient clinics was reduced (2). In the letter of the Ministry of Health dated 16.03.2020 on 'Postponement of Elective Procedures and Other Measures to be Taken'; Planning non-urgent elective surgical procedures to a more convenient date as much as possible, encouraging patients who do not have an emergency to receive service primarily from family physicians, ensuring that the current reports of patients with a temporary disability report whose report period has expired will be considered valid until the end of May 2020 and that they will not apply to hospitals to renew their report. It was also announced that medicines, medical supplies and diapers that require regular use due to chronic diseases and disabilities can be obtained from pharmacies and medical doctors without the need to write a prescription without going to a health institution (3). On March 20, 2020, a circular was published by the Ministry of Health stating that all hospitals with sufficient specialists and third-level adult intensive care beds are considered pandemic hospitals. This

Cite this article: Erdem M, Kara B, Armağan Karadeniz S. Comparison of effectiveness indicators before and during the COVID-19 pandemic in a university hospital. Interdiscip Med J. 2024;15(52):60-66. https://doi.org/10.17944/interdiscip.1444084

Corresponding Author: Mehmet Erdem: Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Public Health, Hatay, Türkiye
Email: dr.m_erdem@hotmail.com
ORCID iD: 0000-0001-5671-1213

Received: Feb 28, 2024
Accepted: May 25, 2024

situation caused an increase in workload, especially in the emergency departments and intensive care units of hospitals with intensive care beds (4). On March 21, a circular was published stating that those aged 65 and over and those with chronic diseases were prohibited from leaving their residences (5). All these situations have caused the number of non-emergency outpatient clinic patients to decrease.

Hospitals play an important role in meeting the health needs of the society. In addition to providing health services to the society, they are important in

that they constitute the largest share of total health expenditures (6). Today, increased access to health services and the understanding of providing more qualified health services have necessitated the effective use of resources. One of the most important performance indicators used to evaluate hospital services is to reveal how effectively hospital beds are used. The concept of activity, human, financial, technological, etc. It is an evaluation criterion that shows to what extent input elements are used effectively or adequately in line with the determined purposes (7).

In this regard, integrating existing or created resources into the best use to meet the needs will ensure efficiency in service delivery. Effective use of hospital beds is defined by different criteria in various sources. Philip et al. (8) and Ağırbaş (9) studies, "capacity utilization" in the report published by the Ministry of Health in 2011, "productivity indicators (10), Avcı et al. "operational performance indicators" (11), Lotfi et al. "performance measures" (12), Vashishth et al. They preferred to use expressions such as "hospital bed use" (13).

Our aim in this study is to analyze the hospital efficiency indicators in a University Hospital; bed occupancy rate, average patient stay, inpatient rate, bed turnover rate, bed turnover interval, total number of patients applying to outpatient clinics and emergency departments, number of deaths, etc. It is to reveal to what extent the data changed between (2018-2019) before the pandemic and (2020-2021) during the period when the pandemic started and continued.

METHOD

The research is a retrospective and descriptive research. The data belongs to the years 2018-2021 and was taken from the statistics unit of Hatay Mustafa Kemal University Hospital, and the data are in the form of monthly results covering the 4 years of in this study. The study includes data on the number of working personnel, the number of applications to outpatient clinics and emergency departments, and the number of deceased patients between 2018-2019 (before the pandemic) and 2020-2021. As bed use efficiency indicators; Bed occupancy rate, inpatient rate, average patient stay day, bed turnover rate and bed turnover interval were used. Ethics committee permission for the study was obtained from Hatay Mustafa Kemal University Nonclinical Research Ethics committee (Date: 17.03.2022, decision no: 25).

Bed occupancy rate; It shows the rate at which patient beds are used by patients within a certain period of time (one month, three months, one year, etc.). It reflects the popularity of hospitals in terms of inpatients [14].It is considered positive that the bed occupancy rate is 80-85% in general hospitals and 90-95% in hospitals treating chronic diseases. It is calculated with the formula (Number of Days Stayed x 100) \ (Number of Beds x 30).

Inpatient rate; It is an efficiency ratio that shows how many patients who applied to hospital outpatient clinics were hospitalized and treated within a certain period of time. The rate varies by hospital type. In a health system where the referral system functions well, the rate of inpatients is expected to be high. The inpatient rate, which shows how many patients applying to hospital outpatient clinics are treated as inpatients, has been observed to be low in places where the health infrastructure is inadequate. It is calculated with the formula (Number of Inpatients) \ (Number of Polyclinics).

Average patient stay day; It is the measure obtained by dividing the total number of days spent (on a clinic basis) by the total number of discharged (discharged and deceased) patients within a certain period (month, three months or a year). This criterion is an indicator used to evaluate the use of health services and the quality of service provided in the hospital. In addition to reflecting the change in service provided in the hospital, the average length of stay is also important in that it provides data on seasonal change. Situations such as the presence of epidemic diseases and tourism activities also provide data about seasonal changes in hospital services. It is calculated with the formula (Total Patient Days) \ (Number of Discharged Patients).

Bed turnover rate; It shows the patient bed efficiency level by how many patients use the bed in a certain period of time. There is a relationship between bed turnover rate and hospital size. For example, university hospitals with high bed capacity generally operate at higher capacity. A low bed turnover rate may not only indicate that the hospital is preferred by fewer patients or that patients are kept in the hospital unnecessarily, but it may also indicate that difficult and complicated diseases are treated in these hospitals. A high bed turnover rate may indicate that simple first aid treatments are provided by the hospital.It is calculated by the formula: Number of Inpatients (excluding Intensive Care) / Actual Number of Beds (excluding Intensive Care Bed Numbers)

Bed turnover interval; It is the measure that shows

the average number of days a patient bed remains empty between two patient admissions. Leaving a patient bed empty is considered inefficiency. Therefore, what is desired is that the time between two patient admissions is short. Although it is desirable to keep the bed turnover interval short, keeping it too short or constantly giving negative feedback about the quality of the service provided. Because low utilization level of hospital facilities indicates low turnover interval. It is calculated by the formula Bed Turnover İnterval= ((Hospital bed x number of days in the relevant period) - Number of days hospitalized) / (Number of discharged patients + Number of patients who died), (14).

In statistical analyses, numbers by month and the monthly average and standard deviation of hospital indicators by year were calculated as descriptive statistics. Spearman correlation analysis was performed between the monthly case numbers reported by Turkey to the World Health Organization (15) and the effectiveness indicators of the hospital under investigation.

RESULTS

Distribution of healthcare personnel in the hospital where the study was conducted is shown in **Table 1.** The total number of beds in the hospital in 2018, 2019 and 2020 is 503. While the total number of beds was 503 in January 2021, it later increased to 608. The number of adult intensive care beds in 2018, 2019 and 2020 is 52. The number of adult intensive care beds, which was 52 in January 2021, later increased to 72.

Table 1. Number of personnel by years

Year	Lecturer	Assistant Doctor	Nurse
2018	119	136	295
2019	111	137	350
2020	156	249	391
2021	157	254	463

In all years examined, the minimum number of emergency applications was in April 2020 (n = 1287) and the maximum in January 2020 (n = 8288). While the number of outpatient clinic admissions to the hospital was lowest in April 2020 (n=7530), the highest was seen in January 2020 (n=59642), **(Figure 1).**

The 12-month averages of hospital indicators for the four years examined were calculated. The highest bed occupancy rate by year was observed in 2020 with 77.2±6.7. The highest inpatient rate was in 2020 with 6.7±2.1, the highest average day of stay was in 2021 with 10.8±2.2, the highest bed turnover rate was in 2020 with 3.9±0.9, and the highest average day of stay was in 2021 with 3.9±0.9. The bed-to-bed turnover interval was found to be 5.2±2.2 in 2021 **(Table 2).**

During the years examined, the highest bed occupancy rate was in October 2019 with 92.9%, the highest inpatient rate was in April 2020 with 11.8%, the highest average day of stay was in October 2021 with 13.8, the highest bed turnover rate was in October 2021 with 11.8%. The turnover rate was 5.3 in January 2020, and the highest bed turnover interval was 16.8 in April 2020.

Mean±SD (Mean±Standard Deviation),* The average of 12 months was calculated

Table 2. Bed occupancy rate, inpatient rate, average day of stay, bed turnover rate and bed turnover interval by years

	Bed occupancy Rate	Inpatient Rate	Average Day of Stay	Bed Turnover Rate	Bed Turnover Interval
	Mean±SD*	Mean±SD*	Mean±SD*	Mean±SD*	Mean±SD*
2018	43,7±9,1	5,6±0,5	5,8±1,5	4,7±0,3	7,9±1,7
2019	77,2±6,7	4,4±0,3	5,2±1,9	4,7±0,3	1,4±0,3
2020	70,6±12,5	6,7±2,1	9,3±2,2	3,9±0,9	4,7±4,5
2021	68,3±7,5	6,4±0,5	10,8±2,2	3,9±0,6	5,2±2,2

*SD: Standart deviation

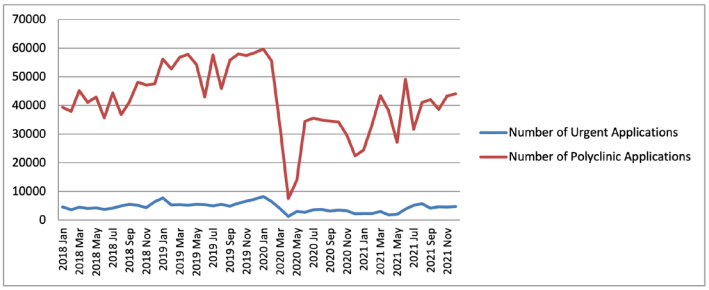

Figure 1. Monthly Numbers of Emergency and Polyclinic Applications to the Hospital Between 2018-2021

According to years, the highest intensive care bed occupancy rate was observed in 2020 with 92.8±12.7, and the highest intensive care average patient stay was observed in 2021 with 2343.3±234.0. When we look at the surgical service bed occupancy rates by year, the year with the highest rate was 2019 with 81.9±9.2, and when we look at the internal service bed occupancy rate, the year with the highest rate was 2019 with 70.1±8.2 **(Table 3)**. When all years are analyzed by month, the lowest total intensive care bed occupancy rate is 35.9% in June 2018, and the highest total intensive care bed occupancy rate is 100% in May, June, July, September, October and November 2020.

Mean±SD (Mean±Standard Deviation),* The average of 12 months was calculated

Table 3. Intensive care, surgical Service, internal service bed occupancy rate and intensive care average patient stay day by years

	Intensive Care Bed Occupancy Rate	Intensive Care Average Patient Stay Days	Surgical Service Bed Occupancy Rate	Internal Service Bed Occupancy Rate
	Mean±SD*	Mean±SD*	Mean±SD*	Mean±SD*
2018	52,1±12,7	1025,3±203,4	46,2±6,9	36,1±11,9
2019	82,8±5,9	1742,2±124,5	81,9±9,2	70,1±8,2
2020	92,8±9,2	1951,0±276,0	68,3±15,5	65,2±12,6
2021	90,1±6,1	2343,3±234,0	67,8±8,9	61,2±9,9

*SD: Standart deviation

Number of patients who died from January 2018 to December 2021 **in Figure 2** can be seen. The average number of deceased patients in 2018, 2019, 2020 and 2021 is respectively 45±13, 52±12, 36±10 and 32±7.Spearman correlation analysis was performed for 2020 and 2021 between the monthly number of cases reported by Turkey to the World Health Organization since the beginning of the pandemic and the monthly indicators of the hospital under investigation. Moderate positive correlation between the number of cases and the inpatient rate (R = 0.446**, p=0,029**) and a strong positive correlation was detected between the monthly number of cases and the day of intensive care stay (R = 0.661, p<0,001).

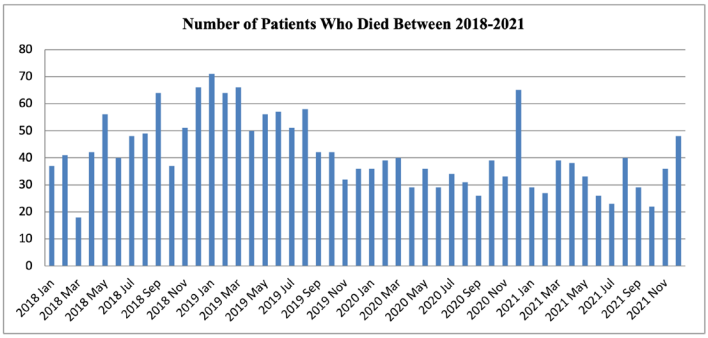

Figure 2. Number of Deaths of Patients by Month Between 2018 and 2021

DISCUSSION

A rapid increase in emergency applications was detected in October, November and December in 2018 and 2019, the pre-pandemic period. It can be thought that the important reason for the increase detected in these months is the increase in the frequency of upper respiratory tract infections. A similarity was found between our findings and the research conducted by Kuşkucu et al. at Istanbul University Cerrahpaşa Faculty of Medicine in 2020 (16). In this study, serious decreases have been observed in the number of emergency applications since January 2020, when Covid-19 started to spread rapidly around the world, and March 2020, when it was first seen in Turkey. In the study conducted by Alataş et al. in 2021 at Muğla Sıtkı Koçman University Training and Research Hospital during the pandemic period, it was found that the number of patients applying to the emergency department decreased (1). At the same time, the fact that the number of patients applying to the emergency department in the pre-pandemic years was higher than the number of patients applying to the emergency department during the pandemic period can explain why the Covid-19 pandemic caused a decrease in the number of patients applying to the emergency room.

It was determined that the lowest number of outpatient clinic applications in the last four years was in April 2020, and it is seen that the Covid-19 pandemic caused a decrease not only in the number of emergency applications but also in the number of all outpatient clinic applications. In the study titled 'Evaluation of Health Services Use during the Covid-19 Pandemic Period', conducted by Yıldız et al. at Batman University in 2021,a decrease was observed in the number of outpatient clinic applications during the Covid-19 period (17). It can be said that the decrease in the number of outpatient clinic applications in April 2020 was caused by some restrictions imposed during the pandemic period. As an example, a curfew was imposed on individuals over the age of sixty five on March 21, 2020, and on individuals under the age of twenty on April 3, 2020, and it is possible to give these restrictions to continue throughout April. At the same time, the reduction in public transportation capacities by half on March 24, 2020, and the continuation of this situation throughout April may have caused difficulties in transportation to the hospital, which may have caused the decrease in the number of applications to polyclinics (18).

Bed occupancy rate is considered a basic efficiency indicator as it determines the hospital's utilization level and productivity. This rate is a measure of the efficient use of hospital beds. It would be useful to evaluate this efficiency criterion together with criteria such as average patient stay and bed turnover rate. The Ministry of Health has accepted the bed occupancy rate as 72% and the average day of stay as 4.5 days as an efficiency indicator in training and research hospitals. A low average day of stay is a good indicator, but a large decrease is interpreted negatively (19). Bed turnover interval also affects bed occupancy rates, and it has been seen in the literature that there may be decreases in bed occupancy rates if there is idle capacity in hospitals (20). When we examined the years before the pandemic, the bed occupancy rate in 2018 was found to be 43.4% and remained below the Ministry of Health's productivity indicator. We can explain this situation in this study with the shortage of healthcare personnel and nurses in 2018. In the study titled Examination of human resources in the health sector in Turkey, conducted by Özkan et al. at Marmara University in 2015, the need for nurses and auxiliary health personnel was mentioned and the importance of studies to meet this need was emphasized

(21). At the same time, the high value in the bed turnover range is another factor in the low bed occupancy rate. In this study, the bed occupancy rate in 2019 was found to be 77.3% and exceeded the value determined by the Ministry of Health. This situation may be related to the increase in the number of staff and nurses working in our hospital, but it may also be due to the effect of the bed turnover interval, which has decreased significantly compared to the previous year.

With the pandemic, an increase in the rate of inpatients and an extension in the average day of stay were detected. A decrease in the bed turnover rate may be observed as the average day of stay becomes longer. The increase in the average day of stay above the accepted value and the decrease in the bed turnover rate negatively affected the bed occupancy rate during the pandemic period of 2020. In 2021, when the pandemic continues, the increase in the average day of stay and bed capacity compared to the previous year can be explained as the reason for the decrease in bed occupancy rate.

Surgical service bed occupancy rates increased significantly in 2019 compared to 2018. It is thought that the increase in the number of nurses and healthcare personnel and the increase in the number of surgeries performed played an important role in this large increase. During the pandemic period, the surgical service bed occupancy rate decreased compared to the previous period. This situation can be explained by the postponement of elective surgeries and the infection control measures notification announced by the Ministry of Health in our country (22). In case of emergency and oncological surgery, early discharge is important in order to reduce the exposure of patients and healthcare personnel to the virus and to use beds, ventilators and other hospital resources appropriately. This situation brought the "Accelerated Recovery After Surgery" protocols to the agenda. With why these protocols, a significant decrease was recorded in the number of days spent in the hospital in April 2020. On March 9, 2021, the guide titled 'Study Guide and Infection Control Measures in Health Institutions during the COVID-19 Pandemic' was published. With the update, postponed elective surgeries started to be performed gradually. In this way, the number of surgeries performed in March 2021 and later, and accordingly the surgical service bed occupancy rate, remained at normal levels (60-80%).

It is very important to what extent the intensive care bed potential is used in hospitals. Low bed occupancy rate causes personnel costs to remain high compared to the service provided and existing potential cannot be used efficiently. In Turkey, acceptable intensive care ICU was determined as 85% in the efficiency scorecard indicator cards of the Ministry of Health (23). The average intensive care bed occupancy rate in our hospital in 2018 is below the acceptable value with 52.1. In 2019, this rate increased to the normal level of 82.8. In the next two years, the intensive care bed occupancy rate continued at acceptable levels. With the onset of Covid-19 cases in Turkey, the intensive care bed occupancy rate remained at 100% from April 2020 to November 2020.

When the data on the number of patients who died between January 2018 and December 2021 is examined, the post-pandemic months of December 2020 and 2021 are the months with the highest number of deaths in both years. However, the number of emergency applications and outpatient clinic applications in December 2020 and 2021 are below the number of applications in the same months of previous years. Although the number of applications is low, the number of deceased patients is high, which may suggest that people with Covid-19 infection and comorbid chronic diseases apply for emergency and outpatient clinic examinations. Similarly, the fact that the number of days spent on the same dates was higher than in other periods may have been effective in the increase in the number of deaths. Various studies emphasize that mortality increases as the duration of hospitalization increases. In the study conducted by Ceylan et al. in 2001, no difference was found between prolonged hospital stay and mortality, but complications were found to increase in patients hospitalized for more than 14 days (24). In the study conducted by Craven et al., it was reported that the relative risk of mortality was 3.2 times higher in patients with a hospital stay of more than 10 days (25). In a study conducted by Kölgelier et al. at Adıyaman University in 2012, it was stated that as the length of stay in the ICU increased, the effect of infections on mortality was mentioned, but no direct relationship was found between mortality and length of stay (26).

CONCLUSION

A number of indicators are used to measure the performance and efficiency of hospital services. These indicators include bed utilization activities related to the hospital's capacity utilization. With this in mind, the bed utilization efficiency of the relevant hospital was evaluated within the scope of the study. Accurate analysis of the hospital's capacity utilization and the efficiency indicators evaluated in the study should be considered as a whole. As a result of the analysis; While there was a decrease in the bed occupancy rate compared to the previous year during the pandemic period, there was an increase in the rate of inpatients and the number of days spent. During the pandemic period, the intensive care bed occupancy rate remained high and 100% occupancy was detected during the peak period throughout the country. During the pandemic period, a decrease was detected in the number of emergency room applications, polyclinic applications, and surgical service bed occupancy rates due to only emergency surgeries

being allowed. During the pandemic, there was an increase in the number of days spent in intensive care compared to the previous period. While the number of applications to the outpatient clinic decreased during the pandemic, an increase in the hospitalization rate of patients was detected. While the bed turnover rate decreased, an increase in the death rate was observed.

As a result, efficient use of hospital beds is of great importance for hospitals and patients, especially in situations such as unexpected pandemics. In this regard, in hospitals; Taking precautions and decisions as quickly as possible, considering that they will be negatively affected by the pandemic, increasing the number of intensive care beds, increasing the Emergency Department service capacity, increasing the number of doctors, nurses and staff working in intensive care and emergency, constantly evaluating hospital efficiency indicators by hospital managers and making rapid plans. We consider being prepared for the rapid supply of necessary equipment, taking the necessary precautions to prevent emergency surgeries from being interrupted, arranging operating procedures and keeping all hospital committees, especially the infection committee, in communication with each other and all similar practices as recommendations that should be taken in terms of pandemic management.

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

Ethical permission was obtained from the Ethics committee permission for the study was obtained from Hatay Mustafa Kemal University Non-Interventional Clinical Researches Ethics Committee (Date: 17.03.2022, decision no: 25) and Comparison of effectiveness indicators in Covid 19. Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: ME, BK Design: ME, BK, Supervising: SAK, Financing and equipment: ME, Data collection and entry: SAK, BK Analysis and interpretation: SAK, ME Literature search: ME, BK, SAK, Writing: ME, Critical review: ME

Thanks

We would like to thank Hatay Mustafa Kemal University Faculty of Medicine Intern Doctors for their contribution to the study; Saime Ezgi Yalçındag, Evin Sincaroglu, Kubra Kaya, Begum Unlutaskiran, Muhammet Yagız Ibiloglu, Gullu Akbas, Feyza Nur Bastik, Hande Tunc, Almira Aggul, Elif Yaltirik, Esra Toplan, Murat Baran Yasar, Aslihan Uygun, Betul Eronu, Zeynep Kara.

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1458883
Interdiscip Med J 2024;15(52):67-71

Effectiveness of negative pressure wound therapy as a fixator in split thickness skin graft applied diabetic patients: evaluation of 25 cases

Fatih Ceran[1], Emin Kapi[2], Mehmet Dokur[3]

[1] Biruni University School of Medicine, Department of Plastic, Reconstructive and Aesthetic Surgery, İstanbul, Türkiye
[2] University of Health Sciences, Adana Faculty of Medicine, Health Application and Research Center, Department of Plastic, Reconstructive, and Aesthetic Surgery, Adana, Türkiye.
[3] Biruni University School of Medicine, Department of Emergency Medicine, Istanbul, Türkiye

Abstract

Effectiveness of negative pressure wound therapy as a fixator in split thickness skin graft applied diabetic patients: evaluation of 25 cases

Objective: Microangiopathies expose diabetic patients to lower extremity wounds at certain stages of their lives. Split-thickness skin grafting (STSG) has an important place in the surgical treatment of such wounds. The aim of the present study is to evaluate the effects of negative pressure wound therapy (NPWT) on STSG survival.
Methods: A total of 25 diabetic patients (M = 20, F = 5) with acute or chronic lower extremity open wounds were included in the study. All patients underwent wound debridement under regional anesthesia. STSG was applied after wound debridement. NPWT was applied to STSG to increase graft survival.
Results: The hospitalization times of the patients ranged from 1 to 2 weeks. The mean follow-up period of the patients was 6 months. All wounds healed on the 14th postoperative day. There was no recurrence in the 6-month follow-up period.
Conclusion: We objectively demonstrated the positive effects of NPWT application on STSG and graft survival.
Keywords: Negative pressure wound therapy, Skin grafts, Diabetic patients

INTRODUCTION

Diabetic patients may encounter lower extremity wounds throughout their lives, which often become intractable and complicated for both the patient and the physician (Figure 1). Researchers have described various dressing treatments for treating lower extremity wounds in this patient group (1,2). Researchers have also proven the effectiveness of hyperbaric oxygen therapy (3). However, in most cases, surgical procedures are eventually required. Surgical methods frequently used include split-thickness skin grafts (STSG) and various local and distant flap applications following wound debridement (4).

A common technique for wound care is negative pressure wound therapy (NPWT). This approach involves applying NPWT sponges to the clean wound bed and connecting them to a device that provides continuous or intermittent negative pressure (5,6). NPWT keeps the wound bed clean and accelerates granulation and revascularization. Recent studies have investigated the protective use of NPWT in STSG-applied areas. Applying the sponge to the STSG area wraps the graft and secures it to the wound bed, thereby preventing graft shearing. In addition, it reduces the rates of seroma, hematoma, and infection, which are the biggest obstacles to STSG adaptation (7-9).

This study aimed to evaluate the efficacy of NPWT in patients with diabetic lower extremity wounds who underwent STSG retrospectively.

METHOD

The study included a total of 25 diabetic patients (20 males and five females) with acute or chronic open lower extremity wounds admitted to the Department of Plastic and Reconstructive Surgery of Batman State Hospital between November 2017 and August 2020. All informed consents

Cite this article: Ceran F, Kapi E, Dokur M. Effectiveness of negative pressure wound therapy as a fixator in split thickness skin graft applied diabetic patients: evaluation of 25 cases. Interdiscip Med J. 2024;15(52):67-71. https://doi.org/10.17944/interdiscip.1458883

Corresponding Author: Fatih Ceran, Biruni University School of Medicine, Department of Plastic, Reconstructive and Aesthetic Surgery, Istanbul, Türkiye.
Email: fatihcrn@hotmail.com
ORCID iD: 0000-0003-3403-1457

Received: Mar 25, 2024
Accepted: Jun 10, 2024

were obtained. The study received approval from the Adana City Hospital Clinical Research Ethics Committee, bearing the date and decision number 2022/2321. We conducted this study adhering to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments. The study included patients with open lower extremity wounds and adequate blood supply to their lower extremities. We excluded patients with amputation indications and those who had undergone flap application. We collected samples for culture from all patients admitted to the clinic and arranged their treatment. All patients underwent wound debridement with regional anesthesia. Following wound debridement, we attached the removed STSG from the thigh to the defect using a stapler. We applied Chlorhexidine acetate-impregnated tulle grass (Bactigras®, Smith & Nephew Medical Ltd., Hull, England, UK) and NPWT (Renasys®, Smith & Nephew Medical Ltd., Hull, England, UK) to the STSG. We operated the NPWT at constant pressure and in continuous mode. We closed the graft donor site with chlorhexidine acetate-impregnated tulle grass. We opened and checked the wound site on the 3rd postoperative day, followed by a repeat application of NPWT. The postoperative 6th day saw the termination of NPWT and the continuation of the tulle grass dressing. The postoperative 14th day saw the opening of all areas.

Statistical Analysis

The research data was analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 22.0 program (IBM Corp., Armonk, NY, USA). We evaluated the data using descriptive statistical methods such as number, percentage, mean, and standard deviation. We examined the kurtosis and skewness values to determine whether the research variables showed a normal distribution. The variables' kurtosis and skewness values are considered to have a normal distribution if they are between +1.5 and -1.5 (Tabachnick and Fidell) and +2.0 and -2.0 (George and Mallery). We determined that the variables displayed a normal distribution. We analyzed the data using parametric methods. The Chi-Square test analyzed differences between the proportions of categorical variables in independent groups. We used the t-test to compare quantitative, continuous data between two independent groups.

RESULTS

The mean age of the patients included in the study was 48.2 years (range: 41–58). There were 20 males and five females. The average hospitalization duration of the patients was 8.960±2.441 days (range: 7–14), and the mean follow-up period was six months. On the 3rd postoperative day, when we opened the NPWT, we observed minimal seroma formation at the border of the graft in 8 patients (32.0%). We applied NPWT after the drainage procedure. In those seroma formations, four patients (16.0%) experienced partial graft failure at the wound edges. The 6th postoperative day revealed that all grafts had adapted. We discontinued the NPWT therapy at this point. We continued the tulle grass dressing in the following days to protect the grafts. The average healing period of the patients is 9.920±2.139 days (range: 7–14) (Table 1). The 6-month follow-up period revealed no recurrent wound formation (Figure 2).

Table 1. Characteristics of patients with diabetic foot wounds

Parameter	(n)	(%)
Gender		
Male	20	80.0
Female	5	20.0
Seroma formation	8	32.0
Partial graft failure	4	16.0
Total graft failure	0	100
Long term reccurence	0	100
Durations (Mean±SD)		
Healing period (day)	9.92±2.13	
Hospitalization duration (day)	8.96±2.44	

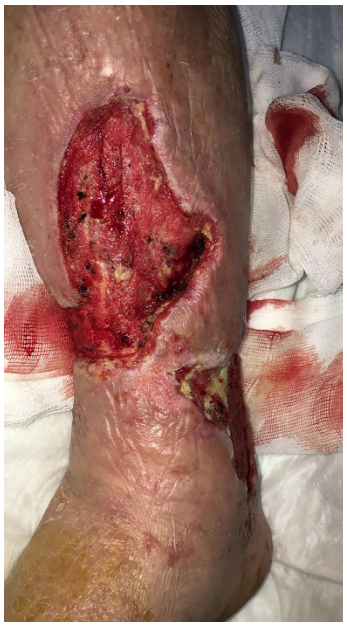

Figure 1. Patient's preoperative view

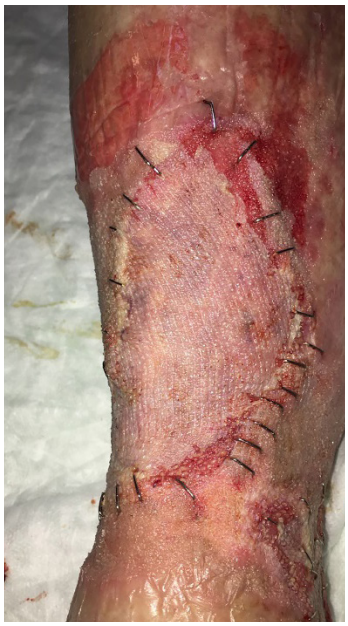

Figure 2. Patient's postoperative view. The graft fully conforms to the wound bed

There is a significant difference in patients with seroma formation depending on the occurrence of partial graft failure ($\chi 2 = 10.19$; $p = 0.006$) (Table 2).The healing period varies significantly depending on the seroma formation status of the patients ($t(23) = 6.472$; $p = 0.000$).

The healing period of seroma formation positive patients (X=12.380) was found to be higher than that of seroma formation negative patients (X=8.760). Hospitalization duration varies significantly depending on the seroma

formation status of the patients (t(23) = 5.688; p = 0.003). Hospitalization duration of seroma formation positive patients ($\bar{x}$=11.620) and seroma formation negative patients' hospitalization duration ($\bar{x}$=7.710) were found to be high (Table 3).

Table 2. In those seroma formations, four patients experienced partial graft failure at the wound edges

Parameter n		Positive		Negative		Total		p value
		%	n	%	n	%		
Partial Graft Failure	Positive	4	%50.0	0	%0.0	4	%16.0	χ^2=10.119 p=0.006
	Negative	4	%50.0	17	%100.0	21	%84.0	

Table 3. Hospitalization duration and healing period of patients with diabetic foot wounds who developed seroma formation

Parameter	Positive (n=8)		Negative (n=17)		t	p value
	Mean	SD	Mean	SD		
Healing Period	12.380	1.506	8.760	1.200	6.472	<0.001
Hospitalization Duration	11.620	2.560	7.710	0.920	5.688	0.003

DISCUSSION

The concept of angiogenesis and healing with mechanical forces dates back to 1911 (10). After World War II, the 'envelope technique' was used (11). The NPWT technique, on the other hand, gained popularity in 1997 after Argenta and Morykwas' study of a new method for wound control and treatment (5). Recent years have seen a comparative investigation into the effectiveness of wound healing interventions for chronic foot ulcers in diabetes (6).

A sponge, a connection apparatus, and a device that produces negative pressure make up NPWT. For the last two decades, its use in managing open wounds has been widespread. Primarily, it speeds up the granulation and revascularization of open wounds, while also reducing the risk of infection development. Subsequent studies have suggested that NPWT application on the graft may be beneficial after STSG, yielding successful results (7, 12). More research supported these findings and found that NPWT treatment on STSG stopped graft mobilization and the formation of seroma and/or hematoma, which increased graft survival (13–15). The present study evaluated this basic principle. We applied NPWT to the graft as a bolster dressing after debridement and STSG application in 25 patients with open lower extremity wounds that did not require flap application.

Seroma and hematoma formation can be considered the leading causes of graft loss. Similarly, previous practices of applying dressings after graft adaptation could lead to the mobilization and shifting of the graft. Moreover, the mobilization of the patients may also trigger the mobilization of the grafts. Therefore, immobilization is required, especially after STSG applications to the extremities (7, 12). In this study, the application of NPWT on STSG eliminated the need for immobilization, so we did not use splints after the treatment. We opened the NPWTs on the 3rd postoperative day and evaluated the graft survival. In diabetic patients, total or near-total graft loss can often occur due to impaired wound healing. In 8 patients, we observed graft-wound border-located minimal seroma formation, which regressed following drainage and re-application of NPWT, yielding satisfactory results in all patients. It is very possible for partial graft loss to occur at the wound margins. Often, this area serves as the junction point between the graft and the wound lips, where disruption of wound-graft contact can occasionally occur. However, only 4 of in this patients experienced partial graft loss at the wound border line, and these areas became epithelialized in a short time.

As a result of microcirculation defects in diabetic patients, acute or chronic wounds occur in the lower extremities. These wounds cause serious labor and economic losses. Previous wound care practices for such patients involved frequent dressings with various materials over an extended period (12). Today, almost all wound care clinics use the NPWT application, which has become widespread (16). In fact, home health agencies in developed countries have introduced disposable negative-pressure wound therapy devices in recent years (17). In a 41-patient cohort study, Sun et al. demonstrated the effectiveness of a new and low-cost negative pressure wound therapy (LC-NPWT) in the treatment of diabetic foot ulcers (DFUs) with Wagner grade 3 DFUs (18) as an alternative to this. Negative pressure wound therapy, with novel techniques, has brought new perspectives to the treatment of not only diabetic foot wounds but also almost all surgical wound infections (19). Besides, Driver et al. reported that the NPWT application is cost-effective for these patients who require long-term treatment (1). Of course, it would be incomplete to evaluate this approach only in terms of cost-effectiveness, since frequent dressing for these patients requires serious healthcare worker effort. Changing the dressing every three days after NPWT application suffices, thereby reducing the effort required for wound care. Diabetes is a disease with multiple systemic components. Hospitalization often focuses solely on wound management for these patients, but other systemic conditions may also surface during this period. During hospital care for such patients, it is necessary to collaborate with other disciplines, such as infectious diseases and microbiology specialists, to plan appropriate antibiotic treatments according to the culture results taken before treatment interventions. Similarly, it is essential to cooperate with the endocrinology department for blood sugar regulation. In short, multidisciplinary work is required to manage wounds in diabetic patients.

Limitations of the study

A relative limitation of this clinical study is the use of a medium-sized patient series.

CONCLUSION

After applying STSG, NPWT significantly increases graft survival. NPWT implementation is cost-effective. A multidisciplinary approach is essential for diabetic lower extremity wounds.

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

Ethical permission was obtained from the University of Health Sciences, Adana City Hospital Clinical / Human Research Ethics Committee for this study with date 2022 and number 2321, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: FC, EK, Design: FC, EK, Supervising: FC, EK and MD, Financing and equipment: FC, EK, Data collection and entry: FC, EK, Analysis and interpretation: FC, EK and MD, Literature search: FC, EK and MD, Writing: FC, EK and MD, Critical review: FC, EK and MD.

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1462456
Interdiscip Med J 2024;15(52):72-79

Evaluation of platelet indices in chronic kidney disease

Mahmut Egemen Senel[1], Ertugrul Erken[2], Ilyas Ozturk[3], Neziha Erken[4], Orcun Altunoren[2]

[1] Necip Fazil City Hospital, Department of Internal Medicine, Kahramanmaras, Türkiye
[2] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, Kahramanmaras, Türkiye
[3] Necip Fazil City Hospital, Department of Internal Medicine, Division of Nephrology, Kahramanmaras, Türkiye
[4] Necip Fazil City Hospital, Department of Internal Medicine, Division of Geriatrics Medicine, Kahramanmaras, Türkiye

Abstract

Evaluation of platelet indices in chronic kidney disease

Objective: Chronic kidney disease (CKD) is characterized by an irreversible decrease in kidney functions and accumulation of uremic toxins in the body. Platelet indices have the potential to predict the inflammatory status and disease progression in patients with CKD. In this study it was aimed to investigate platelet indices and their relations with renal function and comorbid conditions in CKD patients.
Method: In this study it was included 411 CKD patients. We looked for associations between platelet indices and estimated glomerular filtration rate (eGFR). We generated linear regression models for platelet indices that may be associated with eGFR. We evaluated CKD patients for possible associations between platelet indices and comorbid conditions such as diabetes, hypertension, and cardiovascular diseases.
Results: The mean age of CKD patients was 60.5 and the GFR value was 40.1+24.8 mL/min/1.73m2. While the mean platelet count, MPV, PCT, PDW, P-LCR values were lower in the advanced CKD group, hematocrit adjusted platelet count (HAPC), MPV/Lymphocyte ratio and SII parameters were higher in the advanced CKD group ($p<0.05$ for all). In analyzes a positive correlation was detected between eGFR and HAPC, and a negative correlation was detected between MPV/Lymphocyte ratio and eGFR ($p<0.001$ and $p=0.036$). MPV, PCT, PDW, P-LCR and SII index were observed to be higher in diabetic CKD patients ($p<0.05$ for all).
Conclusion: Platelet indices have the potential to provide valuable data about chronic diseases and their complications. MPV/Lymphocyte ratio and HAPC can give an idea about CKD progression. Our findings suggest that elevations in platelet volume indices could be indicative of diabetic nephropathy and increased inflammatory status.
Keywords: Chronic kidney disease, Glomerular filtration rate, Hematocrit-adjusted platelet count, Mean platelet volume, Platelet indices, Systemic immune-inflammation index

INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by an irreversible decline in renal functions, leading to metabolic and hormonal disturbances alongside chronic systemic inflammation. Atherosclerotic heart disease emerges as the principal cause of mortality and morbidity in CKD (1). In advanced stages of CKD, there is an increased risk of bleeding and thrombosis (2). This hemostatic imbalance in CKD patients can be attributed to significant coagulation cascade abnormalities and platelet dysfunction (3). Factors such as elevated inflammation, accumulation of uremic toxins, and impaired signaling molecules are known to adversely affect platelet morphology and functionality (4).

Platelets are disc-shaped elements produced in the bone marrow by megakaryocytes, playing a crucial role in hemostasis. They are involved in plug formation via adhesion and aggregation, as well as in the orchestration of the fibrin meshwork, which is essential for blood clotting (5). Recent research has also highlighted the significant role of platelets in both innate and adaptive immune responses. (6). With the introduction of fully automated hematological analyzers, routine assessments now extend beyond platelet count and plateletcrit (PCT) to include platelet volume indices (7). While these indices were initially used primarily for diagnosing primary thrombocytosis, recent studies have begun investigating their connections to chronic systemic

Cite this article: Senel ME, Erken E, Ozturk I, Erken N, Altunoren O. Evaluation of platelet indices in chronic kidney disease. Interdiscip Med J. 2024;15(52):72-79. https://doi.org/10.17944/interdiscip.1462456

Corresponding Author: İlyas Öztürk, Necip Fazil City Hospital, Department of Internal Medicine, Kahramanmaras, Turkey
Email: dregemensenel@gmail.com
ORCID iD: 0000-0003-2829-5050

Received: Apr 1, 2024
Accepted: Jun 3, 2024

diseases. Studies involving platelet indices and specific metrics from blood tests have explored their association with cardiovascular disease (CVD), diabetes mellitus (DM), hypertension (HT), and a range of chronic conditions (8,9,10). The increased risks of systemic inflammation and thrombotic disease in advanced CKD may necessitate to examine the potential links between platelet indices and CKD progression. Although studies evaluating platelet indices in CKD patients have provided some valuable data, there is room for further investigation (6,11,12).

In this study, it was aimed to investigate the potential relationships between the stage of CKD, various clinical indicators, and a broad spectrum of platelet indices. Platelet indices such as platelet count, PCT, mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (P-LCR), hematocrit-adjusted platelet count (HAPC), MPV/Platelet count, MPV/Lymphocyte count, systemic immune-inflammation index (SII) were shown to be associated with various chronic diseases. (10,12,13). We believe that these indices could serve as promising markers for the progression and inflammation related complications of CKD.

METHOD

Case Selection and Data Collection

In this study, it was included that patients over the age of 18, diagnosed with CKD and followed up at the Nephrology Department of Kahramanmaras Sutcu Imam University between 2010 and 2020. Patients with malignancy, cirrhosis, heart failure, thyroid dysfunction, active infection, hematological diseases, severe anemia, and those with systemic inflammatory disease and severe immunosuppression were excluded. All laboratory values were obtained from the health record data bank. The estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (14). Participants were categorized into CKD stages based on their eGFR values. The formula for the HAPC was platelet count x (1/1–Hematocrit), and the formula for the SII was (neutrophil count x platelet count)/lymphocyte count (12). Laboratory values for patients undergoing hemodialysis (HD) were obtained from midweek pre-dialysis blood results. Approval for the study was obtained from the Institutional Medical Research Ethics Committee (Date: 26.08.2020, Session No: 2020/16, Decision No: 09). The study was conducted in accordance with the Declaration of Helsinki.

Data Evaluation

Patients were divided into two subgroups. Patients with eGFR ≥30 mL/min/1.73 m^2 constituted the early-stage CKD group (stages 1, 2, 3a, 3b), and those with eGFR<30 mL/min/1.73 m^2 were placed into the advanced CKD group (stages 4, 5). Demographic data (age, gender, etc.), clinical features (history of chronic diseases, blood pressure, etc.), and platelet indices (platelet count, MPV, plateletcrit, PDW, P-LCR, HAPC, MPV/Platelet count, MPV/Lymphocyte count, SII) were compared between the groups. The effects of comorbid diseases on platelet indices were examined. Correlation analysis was conducted between eGFR and platelet indices. Regression models were generated for the relations between various variables and platelet indices that showed worthy associations with eGFR.

Table 1. Demographics, Clinical Features, and Laboratory Values in CKD Patients

Variable	CKD Patients (n = 411)
Age, *years*	60.5 ± 14.7
Sex, *M/F*; ***n* (%)**	208 (51) / 203 (49)
CKD stage 1/2/3/4/5; *n* (%)	14 (3) / 75 (18) / 171 (41) / 62 (15) / 89 (21)
HD Cases, *n (%)*	47 (11.4)
eGFR, *mL/min/1.73 m^2*	40.1 ± 24.8
DM; *n* (%)	169 (41.1)
HT; *n* (%)	312 (75.9)
CVD; *n* (%)	128 (31.1)
Systolic Blood Pressure, *mmHg*	133 ± 18
Diastolic Blood Pressure, *mmHg*	81 ± 11
Creatinine, *mg/dL*	2.61 ± 2.37
Albumin, *g/dL*	4.16 ± 0.44
Ca x P product, *mg^2/dL^2*	34.1 ± 9.1
Uric Acid, *mg/dL*	6.7 ± 1.9
Hemoglobin, *g/Dl*	12.3 ± 1.9
Platelet Count mean/median, *$x10^6$/ mm^3*	255 ± 75 / 248
MPV mean/median, *fL*	10.4 ± 0.9 / 10.4
Platelecrit mean/median, *%*	0.26 ± 0.07 / 0.26
PDW mean/median, *fL*	12.4 ± 3.6 / 12
P-LCR mean median, *%*	28.4 ± 7.3 / 28.2
HAPC, *$x10^3/mm^3$*	409 ± 120 / 396
MPV/Platelet Count mean/median, *$fL/10^8$ platelet/ cm^3*	4.48 ± 1.62 / 4.15
MPV/Lymphocyte Count mean/ median, *fL/ 10^6 lenfosit / cc blood*	6.33 ± 3.48 / 5.54
SII mean/median, *$x10^6$ cell/mm^3*	800 ± 655 / 641

Abbreviations: CKD, Chronic Kidney Disease; HD, hemodialysis; DM, diabetes mellitus; HT, hypertension; CVD, cardiovascular disease; eGFR, estimated Glomerular Filtration Rate; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; P-LCR, Platelet Large Cell Ratio; HAPC, Hematocrit-adjusted Platelet Count; SII, Systemic Immune-Inflammation Index.

Table 2. Comparisons of platelet indices in early stage (1, 2, & 3) and advanced (4 & 5) CKD patients

Variable	CKD Patients (n=411)		
	Early Stage CKD (n=260)	Advanced CKD (n=151)	p
Age, *years*	61.6 ± 14.6	58.8 ± 14.8	**0.044**
Sex, *M/F*; ***n* (%)**	131 (50) / 129 (50)	77 (51) / 74 (49)	0.905
DM; *n* (%)	108 (42)	61 (41)	0.838
HT; *n* (%)	189 (73)	123 (82)	**0.039**
CVD; *n* (%)	84 (32)	44 (29)	0.515
Creatinine, *mg/dL*	1.36 ± 0,87	4.77 ± 2.59	**<0.001**
eGFR, *mL/min/1.73 m²*	55.0 ± 18.3	14.3 ± 7.6	**<0.001**
Hemoglobin, *g/dL*	12.88 ± 1.77	11.52 ± 1.89	**<0,001**
Albumin, *g/dL*	4.24 ± 0.40	4.03 ± 0.48	**<0.001**
Ca^{+2}, *mg/dL*	9.22 ± 0.65	8.93 ± 0.99	**<0.001**
P, *mg/dL*	3.36 ± 0.61	4.45 ± 1.22	**<0.001**
Ca^{+2} x P product, *mg^2/dL^2*	30.9 ± 5.8	39.6 ± 12.3	**<0.001**
Uric Acid, *mg/dL*	6.60 ± 1.74	6.93 ± 2.21	0.368
Platelet Count, *$x10^6/mm^3$*	261 ± 73	245 ± 76	**0.020**
MPV, *fl*	10.4 ± 0.8	10.2 ± 0.9	**0.031**
Plateletcrit, *%*	0.27 ± 0.07	0.25 ± 0.08	**0.002**
PDW, *%*	12,5 ± 3.0	12.3 ± 4,7	**0.010**
P-LCR, *%*	29.1 ± 7.0	27.3 ± 7.9	**0.031**
HAPC, *$x10^6/mm^3$*	427 ± 118	376 ± 115	**<0.001**
MPV/Platelet Count, *fL/ 10^8 platelet / cc kan*	4.36 ± 1.48	4.68 ± 1.82	0.145
MPV/Lymphocyte Count; *fL/ 10^6 lymphocyte / cc blood*	5.82 ± 2.34	7.22 ± 4.73	**0.007**
SII, *$x10^6$ cell/mm^3*	712 ± 424	951 ± 908	**0.027**

*All of the parameters were non-normally distributed. Abbreviations: CKD, Chronic Kidney Disease; DM, diabetes mellitus; HT, hypertension; CVD, cardiovascular disease; eGFR, estimated Glomerular Filtration Rate; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; P-LCR, Platelet Large Cell Ratio; HAPC, Hematocrit-adjusted Platelet Count; SII, Systemic Immune-Inflammation Index.

Statistical Analysis

All analyses were performed using SPSS version 23.0 (SPSS Inc, Chicago, IL, USA) software. Data were presented as mean and standard deviation (mean ± SD) or percentage (%). The Shapiro-Wilk test was used to evaluate the distribution of the data. Parametric data between two groups were compared using Student's t-test and the Mann-Whitney U test. For non-parametric data comparison, the Chi-square (X^2) test and Fisher's exact tests were utilized. Correlation analysis were conducted using Spearman test. We generated linear regression models for potential influences on the platelet indices. Platelet indices were selected as dependent variable when their correlation coefficients are not very weak.

RESULTS

Demographic Data and Clinical Features in CKD Patients

In this study, it was included that 411 patients diagnosed with CKD. The mean age of the patients was 60.5 ± 14.7. There were 208 women (50.6%) and 203 men (49.4%). DM was present in 169 patients (41.1%). HT and CVD were present in 312 (75.9%) and 128 (31.1) CKD patients. The mean systolic blood pressure (SBP) was 133 ± 18 mmHg, and diastolic blood pressure (DBP) was 81 ± 11 mmHg. The mean creatinine level was 2.61 ± 2.37 mg/dL, and the mean eGFR was 40.1 ± 24.8 mL/min/1.73 m2. Based on eGFR values, 14 patients were classified as stage 1 (3.4%), 75 as stage 2 (18.2%), 171 as stage 3 (41.6%), 62 as stage 4 (15.0%), and 89 as stage 5 (21.6%) CKD. Forty-seven stage 5 CKD patients were receiving HD. When examining hematological parameters of the patients, the mean values for hemoglobin, platelet count and MPV were 12.3 ± 1.9 g/dL, 255 ± 75 $10^3/mm^3$, and 10.4 ± 0.9 fL respectively. The mean PDW and P-LCR were 12.4 ± 3.6 fL, and 28.4 ± 7.3%. The mean HAPC was 409 ± 120 $x10^6$ hc/mm^3, mean value for MPV/Platelet count ratio was 4.45 ± 1.63 fL/10^8 platelets/cc blood, mean MPV/Lymphocyte count ratio was 6.33 ± 3.48 fL/10^6 platelets/cc blood, and the mean SII was 800 ± 655 $x10^6$ hc/mm^3. The demographic characteristics and laboratory results of the patients are presented in **(Table 1)**.

We also evaluated CKD cases in terms of gender and comorbid conditions. The eGFR level was similar between female and male cases (F/M; 40.8±25.9 vs 39.5±23.9 mL/min; p=0.876). The mean hemoglobin level was lower in female cases than in males (F/M; 11.6±1.6 vs 13.1±2.0 g/dL;

p<0.001). Platelet indices such as platelet count, MPV, P-LCR, and SII were found to be higher in women (p<0.001, p=0.01, p=0.024, and p=0.003 respectively). The presence of HT and CAD did not make a difference in terms of platelet indices (p>0.05 for all). In CKD patients with DM (n=169), mean MPV, PCT, PDW, P-LCR, and SII levels were higher compared to those without the dignosis of DM (n=242) (p=0.011, p=0.035, p=0.010, p=0.011, and p=0.006 respectively).

Comparison between Early-Stage CKD and Advanced CKD Groups

Early-stage and advanced CKD groups were compared. Of the total 411 patients, 260 were early-stage and 151 were advanced CKD patients. The mean age of advanced CKD patients was lower, and the frequency of HT was higher in this group (respectively p=0.044 and p=0.039). There was no difference between the groups in terms of the presence of DM and CVD.

The mean hemoglobin value and platelet count were lower in the advanced CKD group (11.52±1.89 g/dL / 12.88±1.77 g/dL) (p<0.001 and p=0.002 respectively). The mean MPV was significantly lower in the advanced-stage CKD group (10.2±0.9 fL / 10.4±0.8 fL) (p=0.031). The mean PCT, PDW, and P-LCR values were also lower in the advanced CKD group (p=0.002, p=0.001, and p=0.031 respectively). While HAPC was lower in the advanced CKD group, the MPV/Lymphocyte count ratio and SII parameter were higher (p=0.001, p=0.007, and p=0.027 respectively). There was no difference in MPV/Platelet count ratio between the groups. Comparisons of clinical data and platelet indices between early-stage and advanced CKD groups are presented in **(Table 2)**.

Correlations Between Platelet Indices and eGFR

When a correlation analysis was conducted between the clinical data and eGFR values, no significant relationship was found between patient age and eGFR. Hemoglobin and albumin values demonstrated a positive correlation with eGFR, whereas the calcium-phosphorus product showed a significant negative correlation. When possible correlations between eGFR and platelet were investigated, weak correlations were observed between eGFR and platelet indices such as platelet count, MPV, PCT, PDW, P-LCR, and SII. Besides, a positive correlation was found between HAPC and eGFR (r=0.253 and p<0.001). More than that, there was a negative correlation between the MPV/Lymphocyte count and eGFR (r=-0.191 and p<0.001). Correlation analysis of eGFR with clinical data and platelet indices in CKD patients is presented in **(Table 3)**.

Evaluation of Clinical Variables That Could Affect Platelet Indices

After examining the data, it was appropriate to conduct multiple linear regression models for possible confounders that could affect HAPC and MPV/Lymphocyte count. In an analysis that was controlled for multiple potential confounders, the positive correlation between HAPC and eGFR persisted **(Table 4)**. According to a similar multiple regression model, we demonstrated that, eGFR decreases significantly along with increasing MPV/Lymphocyte count values **(Table 5)**.

Table 3. Correlation Analysis of eGFR with Clinical Data and Platelet indices in CKD Patients

Variable	eGFR (n=411)	
	R	p
Age	-0.008	0.872
Creatinine	-0.949	**<0.001**
Hemoglobin	0.414	**<0.001**
Albumin	0.276	**<0.001**
Ca^{+2}xP Product	-0.429	**<0.001**
Uric Acid	-0.117	**0.017**
Platelet Count	0.124	**0.012**
MPV	0.108	**0.029**
Plateletcrit	0.157	**0.001**
PDW	0.150	**0.002**
P-LCR	0.120	**0.015**
HAPC	0,253	**<0.001**
MPV/Platelet Count	-0,82	0,099
MPV/Lymphocyte Count	-0.191	**<0.001**
SII	-0.125	**0.011**

*Spearman's rank correlation was used for the non-normal distribution of variables
Abbreviations used: eGFR for estimated Glomerular Filtration Rate, CKD for Chronic Kidney Disease, MPV for Mean Platelet Volume, PDW for Platelet Distribution Width, P-LCR for Platelet Large Cell Ratio, HAPC for Hematocrit-adjusted Platelet Count, SII for Systemic Immune-Inflammation Index.

Table 4. Linear Regression Model Generated for Potential Influences on HAPC in CKD Patients

Variable	B	95% CI	β	p
Age	0.218	-0.568:1.005	0.027	0.585
Gender	20.195	-2,411:42.802	0.086	0.080
DM	-5.941	-29.05:17.17	-0.025	0.613
HD	-47.164	-86.92:-7.41	-0.128	**0.020**
eGFR	1.092	0.55:1.64	0.231	**<0.001**
Albumin	-12.687	-39.07:13.70	-0.048	0.345
Ca^{+2}x P Product	0.917	-0.38:2.22	0.076	0.166

Abbreviations used: HAPC for Hematocrit-adjusted Platelet Count, CKD for Chronic Kidney Disease, CI for Confidence Interval, DM, diabetes mellitus; HD, hemodialysis; eGFR for estimated Glomerular Filtration Rate

Table 5. Linear Regression Model Generated for Potential Influences on MPV/Lymphocyte Ratio in CKD Patients

Variable	B	95% CI	β	p
Age	0.001	-0.019:0.022	0.007	0.891
Gender	-0.279	-0.914:0.356	-0.047	0.389
DM	0.341	-0.257:0.939	0.056	0.263
HD	0.615	-0.411:1.642	0.066	0.239
eGFR	-0.016	-0,031:-0.001	-0.133	**0.036**
Albumin	0.081	-0.639:0.800	0.012	0.825
Ca^{+2}xP Product	-0.025	-0.059:0.008	-0.082	0.142
Hemoglobin	-0.277	-0.471:-0.082	-0.179	**0.005**

Abbreviations: MPV, Mean Platelet Volume; CKD, Chronic Kidney Disease; CI, Confidence Interval; DM, diabetes mellitus; HD, hemodialysis; eGFR, estimated Glomerular Filtration Rate

DISCUSSION

The progression of CKD is interrelated with accelerated atherosclerosis, metabolic abnormalities, and chronic inflammation. In the advanced stages of CKD, the hemostatic balance is adversely affected, increasing the risk for both bleeding and thrombosis. Chronic inflammation and elevated levels of uremic toxins in CKD are well-documented disruptors of platelet functionality. This indicates that platelet index parameters might change as CKD progresses. Although there are studies evaluating platelet characteristics in CKD, very few studies have assessed all platelet indices together (12,16,17). While platelet indices are cost-effective parameters that can be easily measured with automatic hematological analyzers, which platelet index is more beneficial for which chronic disease still remains unclear.

In this study, it was compared that early-stage and advanced CKD patients for all platelet indices. In advanced CKD patients, while platelet count, MPV, PDW, PCT, P-LCR, and HAPC were decreased, the MPV/Lymphocyte ratio and SII were increased. While evaluating the relationships of platelet indices with eGFR, HAPC had a positive relationship with eGFR, yet the MPV/Lymphocyte ratio had a negative one. Additionally, we noted higher platelet volume indices in female patients and those diagnosed with DM.

Although the platelet count is an indicator of the megakaryocyte reserve in the bone marrow the numbers in the peripheral blood are influenced by many factors, including splenic elimination, inflammatory conditions, and anemia (2,18). In this study, even if the platelet counts of our advanced CKD group were lower than those in early CKD stages, both groups had a sufficient number of platelets for hemostatic purposes. It is known that in advanced CKD, it is the functionality of platelets that is affected rather than numbers in the peripheral blood. In line with our findings, there are studies in the literature that reported lower platelet counts in advanced CKD and HD patients (16,19,20). It may be feasible to correct the impact of anemia on platelet number by adjusting the counts with the hematocrit level. HAPC is a parameter acquired by this way. In our CKD patients, HAPC value had a positive correlation with eGFR, even after adjustments for many variables. This correction with hematocrit value might provide a more accurate evaluation of the platelet counts. Hence, we believe that HAPC could be the measure that has the potential to reveal a relationship between eGFR and platelet counts.

MPV represents the mean volumetric measurement of platelets circulating within the bloodstream. While studies examining the relationship between eGFR and MPV have observed increased MPV values in advanced stages of CKD, some studies demonstrated opposite results (17,21,22). Our findings reveal a decrease in MPV values among advanced CKD patients; however, the correlation of MPV with eGFR was weak. PDW, another platelet volume index, indicates platelet anisocytosis. P-LCR quantifies the proportion of platelets larger than 12 fL, offering insights into platelet heterogeneity. In this study, it was observed that a decrease in PDW and P-LCR values in advanced CKD patients. Yu et al. also observed a decrease in PDW and P-LCR values in patients with advanced CKD. Furthermore, they demonstrated that these parameters might also be associated with CVD (12). We believe that a study with a larger sample size could more clearly elucidate the relationship between platelet volume indices and inflammation related clinical implications.

The MPV/Lymphocyte ratio has recently gained attention as an inflammatory marker. Increases in the MPV/Lymphocyte ratio have been shown in acute appendicitis and contrast-associated nephropathy (23,24). A recent study by Bei Xu et al. on pre-dialysis CKD patients indicates that the MPV/Lymphocyte ratio increases with the deterioration of kidney function (25). In this tudy, It was showed that the MPV/Lymphocyte ratio has a negative correlation with eGFR independently of many variables. We interpret this result as a reflection of inflammation

in CKD. We believe that the increase in the MPV/Lymphocyte ratio might be related to CKD progression and thrombotic activity in advanced-stage CKD.

The presence of DM is characterized by hyperglycemia, insulin resistance, increased inflammation, and oxidative stress. These conditions lead to increased platelet production and consumption (13,26). In this study, it was found that CKD patients with DM had significantly higher values of MPV and other platelet volume indices along with PCT and SII levels compared to those without a diagnosis of DM. Previous research indicates that in CKD and DM, the number of activated platelets increase due to chronic inflammation and amplified adhesion molecules (27). A study by Haile et al. suggests that MPV and PDW could be indicators of DM complications (13). Based on these findings, we believe that rises in PCT and platelet volume indices may refer to CKD progression in the presence of diabetic nephropathy.

The relationship between inflammation and CKD has been clearly demonstrated. Therefore, the SII might be useful in monitoring CKD patients. There are studies showing that SII can be associated with albuminuria, CVD, and the presence of CKD (28,29). In this study, it was observed that a significant elevation in the mean SII values among advanced CKD cases when compared to those in the early stages of the disease. We believe that the SII could serve as an indicator of chronic inflammation and its influence on the progression of CKD. Similarly, SII levels were negatively correlated with eGFR, but the strength of the correlation did not reach the level we expected. Therefore, we did not include SII index in our regression models. We believe that further research into the SII index's role in CKD could provide deeper insights into its predictive and diagnostic capabilities.

In this study, it was found that platelet count and some platelet volume indices were increased in females compared to males. These results seem to be consistent with general literature data. In female gender, anemia and hormonal status can also create changes in platelet indices (30,31). With this study, we examined the platelet indices of 411 CKD patients alongside clinical features. We believe our results are valuable due to our good sample size, our assessment of all platelet indices together, and our ability to account for many factors that could affect these parameters. We think that the MPV/Lymphocyte ratio and HAPC can reflect changes in eGFR. Meanwhile, SII index is a promising marker for CKD progression, and the platelet volume indices can reveal subclinical inflammation in CKD patients diagnosed with DM. All these results can be explained by increased platelet destruction, cytokine load, and inadequate thrombopoietin response in advanced-stage CKD (32).

Limitations of the study

The retrospective nature of our study, the absence of a healthy control group, and the inability to evaluate classic inflammatory markers can be considered as limitations of our study.

CONCLUSION

Platelet indices have the potential to provide valuable data about chronic diseases and their complications. MPV/Lymphocyte ratio and HAPC can give an idea about CKD progression. Our findings suggest that elevations in platelet volume indices could be indicative of diabetic nephropathy and increased inflammatory status. Future research will ascertain the importance of platelet indices for CKD and other related chronic conditions.

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 prepared by rearrangement of the doctoral thesis by Mahmut Egemen Senel, entitled as "Evaluation of platelet indices in chronic kidney disease" and the supervisor of the relevant thesis is Ertugrul Erken.

Ethical Declaration

Ethical permission was obtained from the Kahramanmaras Sutcu Imam University, Medical Faculty Clinical Ethics Committee for this study with date 26.08.2020 and number 16/09, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MES, EE, Design: MES, EE, Supervising: MES, EE, Financing and equipment: IO, NE, Data collection and entry: MES, IO, NE, Analysis and interpretation: EE, OA, Literature

search: MES, EE, IO, NE, Writing: MES, EE, Critical review: EE, IO, NE, OA.

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1466355
Interdiscip Med J 2024;15(52):80-85

Investigation of apoptotic efficacy of propolis in MCF-7 cell line

Gülay Gülbol Duran

Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Medical Biology, Hatay, Türkiye

Abstract

Investigation of apoptotic efficacy of propolis in MCF-7 cell line

Objective: Propolis, also known as bee glue, is a resinous compound collected by honey bees from various plants and processed by their saliva enzymes. Propolis and its components have been studied for their cytotoxic effects on cell lines in vitro, and recent studies have shown that they also have an antitumor effect in vivo. This study aimed to investigate the in-vitro apoptotic effects of propolis on the human breast cancer cell line (MCF-7).

Method: The MTT test was used to determine the effect of propolis on cell viability and the doses to be administered. The GraphPad Prism Version 6.01 program was used to analyze the MTT results, while the qRT-PCR method was used to determine the expression levels of Caspase-8, Caspase-9, and Bcl-2 genes. The RT2 profiler PCR Assay Data Analysis version 3.5 was used to analyze gene expression data.

Results: This study it was found that doses of 3.9 and 7.8 µg/ml of propolis showed no cytotoxic effect, while doses of 15.625 µg/ml and above had a cytotoxic effect. There was no change in the expression levels of genes at concentrations of 3.9 µg/ml and 7.8 µg/ml of propolis. However, at 15.625 µg/ml of propolis, Caspase-9 gene expression increased 11.89-fold ($p=0.033$). Although there was no significant difference in Caspase-8 gene expression in the extrinsic pathway of apoptosis ($p=0.437$), a 0.04-fold decrease in anti-apoptotic Bcl-2 gene expression was observed ($p=0.000098$).

Conclusion: In conclusion, propolis showed a dose-dependent cytotoxic effect on the MCF-7 cell line, induced apoptosis, and did so via the intrinsic pathway of apoptosis. The study suggests that propolis has high potential as an anticancer agent since its apoptotic effects have been demonstrated in the MCF-7 cell line.

Keywords: Propolis, MCF-7, Apoptosis, Caspase-9, Bcl-2

INTRODUCTION

Propolis is a resinous bee product manufactured by honey bees *Apis mellifera* L.(1). This natural product, also known as bee gum, is used by bees to repair the hive to keep the temperature and humidity constant by covering the inner surface of the hive and to protect the hive from external factors. Additionally, bees use propolis for hive sterilization (2).There are many active compounds in the structure of propolis, and the composition of the active compounds it contains varies depending on the region and season where propolis is collected (3). Studies have reported that propolis has antibacterial (4-6), antioxidant (7), anti-inflammatory (7), antifungal (8-9), antiviral (10-12), and anticarcinogenic (13-16) effects. Studies conducted in recent years have demonstrated the cytotoxic effects of propolis on cancer cell lines and its anticarcinogenic effects in in vivo studies (17-18). In molecular studies, it has been published that propolis components stop the cell cycle and exhibit anticarcinogenic effects by directing cancer cells to apoptosis (19-20). This effect of propolis has been reported to be due to its anti-proliferative properties, as it arrests the cell cycle in many cancerous cells and induces both death receptor-mediated and mitochondrial apoptosis. (20-21).

Cancer is characterized simply by genetic changes accumulating in the cell and is still one of the most dangerous diseases today (22-23). According to 2020 records, 10 million cancer-related deaths occurred worldwide, and 19.3 million new cancer cases were reported. Among cancer types, breast cancer surpassed the number of lung cancer cases with 2.3 million new cases (11.7%) and was accounted as the most common cancer type (24). Cancer can also be defined as an imbalance between cell gain and cell loss, in which the rate

Cite this article: Duran GG. Investigation of apoptotic efficacy of propolis in MCF-7 cell line. Interdiscip Med J. 2024;15(52):80-85. https://doi.org/10.17944/interdiscip.1466355

Corresponding Author: Gülay Gülbol Duran: Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Medical Biology, Hatay, Türkiye
Email: gulayduran@gmail.com
ORCID iD: 0000-0002-4672-2960

Received: Apr 8, 2024
Accepted: Jun 30, 2024

of increasing mutant tumor cells exceeds the rate of dying cells. Apoptosis, the most well-known form of programmed cell death, is a significant physiological mechanism that limits the expansion of the cell population to maintain tissue homeostasis or to eliminate potentially harmful cells that have persistent DNA damage (25). From the onset of cancer, the apoptosis mechanism is the first process that prevents the proliferation of tumor cells. Apoptosis relies on the activation of different signaling pathways that are frequently released in cancer. Therefore, investigating the apoptotic compounds underlying their expression in carcinogenesis is meaningful and helpful in monitoring the progression of the disease (26).

In this study, it was aimed to investigate whether propolis triggers apoptosis in MCF-7 (breast cancer cell line) cells in vitro, if so, through which apoptotic pathway it occurs and whether it can have an anticarcinogenic effect by causing MCF-7 cancer cells to undergo apoptosis.

METHOD

Cell Culture:

MCF-7 cells, a breast cancer cell line, were used in the experiments. The cell line was obtained from the cell culture stock of Hatay Mustafa Kemal University, Faculty of Medicine, Department of Medical Biology. All experiments were carried out in Hatay Mustafa Kemal University, Faculty of Medicine, Medical Biology laboratories. The cell line was cultivated in DMEM (Dulbecco's Modified Eagle Medium, DMEM, Gibco, UK) containing 10% FBS and 1% penicillin/streptomycin. Incubation of the cells was carried out at 37 °C in an atmosphere of 5% carbon dioxide and 95% humidity. The medium was changed when necessary depending on the change in pH, and it was used in activity studies when the cells grew to cover 70-80% of the culture vessel surface.

Preparation of Propolis:

Propolis samples were supplied from Hatay Mustafa Kemal University, Faculty of Agriculture, Department of Animal Sciences. The propolis extract was obtained by dissolving 300 grams of propolis, which was collected from Hatay province and then powdered, with a 70% ethanol/water solution. The homogenization processes of propolis samples were carried out according to the method described by Mendonca et al (27). Alcohol in the samples was evaporated by shaking in the evaporator for 36 hours at 45 rpm at 50-55 °C. Stock solutions of the propolis were prepared by dissolving solid propolis samples in 1% DMSO.

Cell Viability Analysis:

We performed two separate MTT assays to evaluate the effect of DMSO and propolis on cell viability. Firstly, to determine the non-cytotoxic concentrations of DMSO, the cells were exposed to medium containing different concentrations of DMSO (%1-5) for 24 hours. The cell density used was 1x105 cells/ml, and the experiments were conducted in 24-well plates under specific cultivation conditions, including 95% humidity, 5% CO2, and 37°C temperature. Once the plates reached 70-80% coverage of the culture vessel surface, DMSO dilutions were added to the culture medium and incubated for 24 hours. Following the incubation period, the medium was removed, and 1 mg/ml MTT (Sigma) was added to each well and then incubated for four hours. Next, 0.5 ml DMSO solution was added to each well and incubated at room temperature for five minutes. Then, to detect the colorimetric change, the plates were measured by reading the plates at 590 nm and 670 nm with a spectrophotometer (MultiScan Go, ThermoFisher, Finland). To evaluate the effect of propolis on cell viability, dilutions of propolis in serum-free DMEM medium were prepared at concentrations of 500 - 250 - 125 - 62.5 - 31.25 -15.625 - 7.8 - 3.9 and 0 µg/mL and the above analysis steps were applied.

Table 1. Primer sequences of apoptosis-related genes

Genes	Forward Primers	Reverse Primers
Caspase-8	5'-AGGGCTCAATTTCTGCCTAC-3'	5'-GGCACTGGCTGTTTGCTT-3'
Caspase-9	5'-GTCACAAGACCTTGACACCCG-3'	5'-ACCAGGTGGTCTAGGGGTTT-3'
β-actin	5'-TCAACACCCCAGCCATGTA-3'	5'-AGTACGGCCAGAGGTGTACG-3'
Bcl-2	QuantiTect Primer Assay Cat No: QT00025011, Lot No: 286236904	

Gene Expression Analysis

Propolis dilutions ranging from 15.625 to 3.9 were appended to MCF-7 cells that had grown to cover 70-80% of the culture plates and were treated for 24 hours. At the end of the incubation, total RNA was isolated from the cells using a total RNA isolation kit (Thermo Scientific GeneJET) as per the manufacturer's instructions. The quality and concentration of the obtained RNAs were determined, and the RNA concentration was adjusted to 0.2 µg/µl. Subsequently, cDNA was obtained using the cDNA synthesis kit (Applied Biosystems). The expression levels of Caspase 8, Caspase 9, Bcl-2, and the housekeeping gene β–actin were calculated using the qRT-PCR method (QIAGEN Rotor-Gene Q ,Germany). Gene expressions in MCF-7 cells without propolis added were used as a control group. The primers used for qRT-PCR are given in Table 1. The first denaturation was carried out for 10 minutes at 95°C, followed by qRT-PCR for 40 cycles (15 seconds at 95°C, 60 seconds at 60°C). The expression levels were calculated using the 2-ΔΔCt method, and the results are presented as fold changes.

Statistical analysis

GraphPad Prism Version 6.01 software was used to analyze cell viability assay. Shapiro-Willk test was used to examine whether there is any normal distribution within groups. The Kruskal-Wallis test was performed to compare the differences

among groups. The statistical difference between two groups was determined with Dunn test. Gene expression data was analyzed with RT2 profiler PCR Assay Data Analysis version 3.5 (Qiagen,online service). β–actin house-keeping gene was used for the normalization of the data. The gene expression results were expressed as "fold change" compared to the control group. $p < 0.05$ was considered as significant for statistical comparisons.

RESULTS

Cell Viability

It was determined that 1% DMSO solution did not have a cytotoxic effect on MCF-7 cells (p>0.05) (Figure 1). Considering the effects of propolis samples on cell viability, the concentrations determined by the MTT method were 3.9 and 7.8 µg/ml. There is no statistically significant difference in cell viability between these two concentrations and the control group (p>0.05). Propolis concentrations >15,625 µg/ml were toxic (Figure 2). Cell viabilities were determined as 95.6%, 95.4%, and 79.7% at propolis concentrations of 3.9, 7.8, and 15.625 µg/ml, respectively. When the propolis concentration was increased further (31.25, 62.5, 125, 250, and 500 µg/ml), deeper decreases in cell viability were detected (36.8, 8, 5.4, 6.1, and 2.7%, respectively). For this reason, in gene expression experiments, two concentrations (3.9, 7.8 µg/ml), which were statistically indifferent to the control group cells in terms of cell viability, and propolis concentrations of 15.625 µg/ml, which were above the IC_{50} value, were selected.

Gene Expression

At 3.9 and 7.8 µg/ml concentrations of propolis, Caspase 8 expression, which is involved in the extrinsic apoptosis pathway, was found to be 0.57 and 0.09 fold, respectively. There was no statistically significant difference compared with the control group (p>0.05). At the same concentrations, 0.51- and 0.63-fold increases were detected in the expression of Caspase 9, which is involved in the intrinsic apoptosis

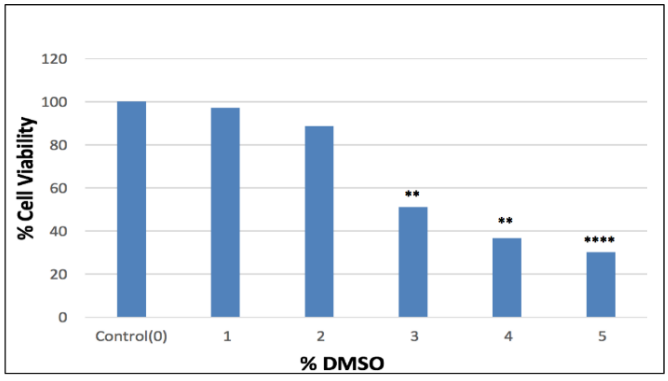

Figure 1. Effect of DMSO on cell viability in MCF-7 cell line. (Statistical significance level: *p<0.05, **p<0.01 and ***p<0.001). *p<0.05, **p<0.01 and ***p<0.001)

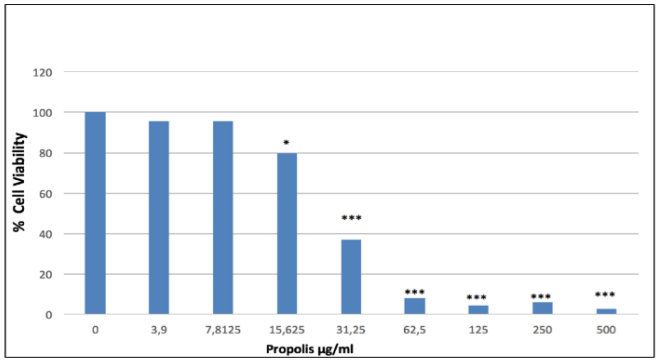

Figure 2. Effect of propolis on cell viability in MCF-7 cell line. (Statistical significance level: *p<0.05, **p<0.01 and ***p<0.001). *p<0.05, **p<0.01 & ***p<0.001)

pathway, respectively. Similarly, there are no significant differences between these groups and the control group (p>0.05). A 1.45-fold and 0.15-fold increase in Bcl-2 expression levels was detected in cells treated with 3.9 and 7.8 µg/ml concentrations of propolis, respectively, and there was no significant difference compared to the control group. Although a decrease was detected in the expression level of cells treated with a propolis concentration of 7.8 µg/ml, it was not statistically significant (p>0.05). When propolis concentration was increased (15.625 µg/ml), the level of Caspase 8 expression was found to increase 0.7-fold, similarly, there is no significant difference with the control group (p>0.05). At the same concentration, an 11.89-fold increase in Caspase 9 expression level was detected. This concentration of propolis significantly increased Caspase 9 gene expression compared to the control group ($p = 0.033$). This propolis concentration (15.625 µg/ml) affected Bcl-2 expression by

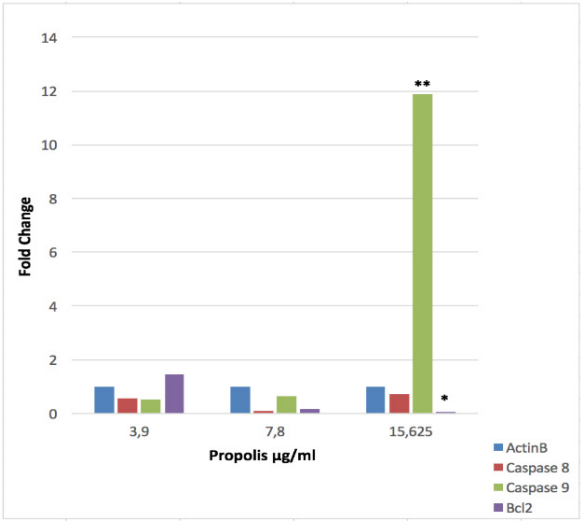

Figure 3. Effect of propolis on the expression levels of apoptotic genes in MCF-7 cell line. (Statistical significance level: *p<0.05, **p<0.01 & ***p<0.001).

0.04-fold, leading to a significant decrease compared to the control group (p = 0.000098) (Figure 3).

DISCUSSION

Breast cancer is one of the leading causes of death among women worldwide. These malignant tumors have very diverse characteristics, including their clinical development, prognosis, and molecular mechanisms (28). According to the latest published cancer statistics of the Ministry of Health of the Republic of Turkey, breast cancer is the most common type of cancer in women (29). In addition to surgical methods, chemotherapy, radiotherapy, and immunotherapy can also be applied in the treatment of breast cancer. However, the majority of patients experience relapses after treatment (30). Moreover, the currently available anticancer drugs have significant problems such as drug resistance and severe side effects, which limit their use (31). Therefore, researchers worldwide are conducting studies on new therapeutic agents of natural origin that are selectively effective against cancer cells. Propolis, a plant-derived honey bee product in the form of resin, is one of many natural products that exhibit anticancer potential. The unique feature of propolis that has attracted the attention of many researchers is that it selectively targets cancer cells, which makes it an alternative to traditional chemotherapeutic drugs (28).

The results of propolis applied in the literature were contradictory. This is because the content of propolis, a natural product, varies depending on the region where it is collected (32). For this reason, the MTT test was taken as the basis for determining the propolis doses to be used. In a study conducted by Amalia et al., it was reported that propolis had a cytotoxic effect on MCF-7 cells (33). In this study, firstly the cytotoxic effects of propolis were examined. Propolis was detected to have a cytotoxic effect on MCF-7 cells at concentrations above 15,625 µg/ml. An inhibition of 20.3% was detected at a concentration of 15.625 µg/ml. It was determined that as propolis concentration increased, the decrease in cell viability increased in direct proportion. Unlike the study conducted by Amalia et al., serious cytotoxic effects were detected even at low propolis concentrations. We think that this difference may be due to factors such as the geographical region where propolis is collected, vegetation, and climatic conditions affecting the composition of propolis. In a similar study by Xuan et al., it was reported that propolis may have a cytotoxic effect on the MCF-7 cell line, depending on dose and time (34).The results of this study are parallel to the study of Xuan et al., and dose-dependent cytotoxicity was detected. The results of another study conducted by Seyhan et al., with propolis samples collected from different countries were also compatible with our findings. In the studies of Seyhan et al., strong cytotoxicity was reported in two different propolis samples at a concentration of 2.5 µg/ml at 24 hours. It has also been reported that cellular apoptosis was triggered in a time-related manner in a sample (35).

Many studies are reporting that propolis has an anti-carcinogenic effect by inducing apoptosis in cancer cells. In a study conducted by Vatansever et al., the MCF7 cell line was treated with various propolis extracts (36). The presence of apoptotic cells was detected using the TUNEL method, and caspase activation was demonstrated through immunohistochemical methods. Mısır et al. reported that propolis induces apoptosis in MCF-7 cells by arresting the cell cycle in the G1 phase, increasing the expression of pro-apoptotic genes, and decreasing the mitochondrial membrane potential (37). Xuan and colleagues reported that propolis induced apoptosis in the MCF-7 cell line. (34). Niyomtham and his colleagues showed in their study that propolis induces apoptosis in the HNSCC (head and neck squamous carcinoma) cell line. (38). Similarly, in the study conducted by Amalia et al., it was reported that propolis initiated apoptosis in the MCF-7 cell line (33). Jiang et al also found that propolis significantly inhibited the growth of human gastric cancer SGC-7901 cells and they reported that it causes cell apoptosis and cell cycle arrest in the S phase, with increased production of reactive oxygen species (ROS) and decreased mitochondrial membrane potential. (20). This study findings, consistent with all these studies in the literature, showed that propolis induces apoptosis in a dose-dependent manner.

Although there are many studies in the literature showing that propolis induces apoptosis in the MCF-7 cell line, no study measuring the expression levels of apoptotic genes has been found. This study is unique by measuring the expression levels of two different caspase genes, which allows distinguishing between intrinsic and extrinsic pathways. It was determined that propolis increased the Caspase-9 expression level by 11.89 times at a concentration of 15.625 µg/ml, while it decreased the expression level of the anti-apoptotic Bcl2 gene by 0.04 times. These results are compatible with all other studies showing that propolis induces apoptosis, as well as showing that it induces apoptosis through the (intrinsic) mitochondrial pathway.

CONCLUSION

The search for natural therapeutic agents with minimal or no side effects in cancer treatment has been ongoing for several years. Propolis is a strong candidate for such a therapeutic agent. In the MCF-7 cell line, it has demonstrated a dose-dependent cytotoxic effect and induced apoptosis through the intrinsic pathway. Its apoptotic effects have been demonstrated in the MCF-7 cell line, which suggests that propolis has high potential as an anticarcinogenic agent. In order to reveal the this potent potential of propolis, further molecular pathway studies in cancer cells need to be carried out.

Limitations of the study

The limitation of this study is that apoptotic cells cannot be demonstrated with more advanced techniques.

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.

Previously Presented

The authors declare that some part of this study was presented as oral presentation at "the XVI. Medical Biology and Genetics Congress" held in Bodrum/Muğla city, entitled as "Investigation of Anti-Carcinogenic Efficacy of Propolis in MCF-7 Cell Line".

Ethical Declaration

Since this study was conducted with commercially obtained cell culture, an ethics committee certificate is not required.

Authorship Contributions

Concept: GGD, Design: GGD, Supervising: GGD, Financing and equipment: GGD, Data collection and entry: GGD, Analysis and interpretation: GGD, Literature search: GGD, Writing: GGD, Critical review: GGD

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ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1496779
Interdiscip Med J 2024;15(52):86-91

Association of cognitive status, anxiety and depression with hearing loss in the elderly

Mehmet İhsan Gülmez[1], Canset Aydın[2]

[1] Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Otorhinolaryngology, Hatay, Türkiye
[2] Atılım University Faculty of Medicine, Department of Otorhinolaryngology, Ankara, Türkiye

Abstract

Association of cognitive status, anxiety and depression with hearing loss in the elderly

Objective: Hearing loss is an important problem that is common among older people. Dementia can be defined as a group of disorders that adversely affect memory, thinking function and the ability to perform daily activities. Hearing loss leads to poor quality of life due to loneliness, social isolation, anxiety and susceptibility to depression. Hearing aids are the primary tool used in the management of hearing loss. In this study, we aimed to compare participants with and without hearing loss in terms of cognitive status, depression and anxiety, and to assess the effect of hearing aid use on this process.
Method: Between June 2023 and June 2024, 608 patients over the age of 50 who registered at the psychiatric outpatient clinic of Hatay Training and Research Hospital were included in the study. Participants were enrolled if they presented to the Psychiatry outpatient clinic during the selected time interval, were over 50 years of age and agreed to participate in the study. Participants' demographic information, educational status, social information, hearing aid use, minimental score, Beck anxiety score, and geriatric depression score were recorded.
Results: When comparing patients with and without hearing loss, statistically significant differences were observed on the Minimental Test, Beck Anxiety Score and Geriatric Depression Score.
Conclusion: In this study, a statistically significant relationship was found between hearing loss and cognitive status, depression and anxiety, and it was suggested that the use of hearing aids may be beneficial in terms of preventing the development or slowing the progression of these pathologies.
Keywords: Anxiety, Depression, Hearing loss, Hearing aid, Dementia

INTRODUCTION

Hearing loss is an important problem that is common among older people. According to the World Health Organization, more than 42% of people over the age of 60 have some degree of hearing loss (1). Dementia is a group of disorders that affect memory, thinking and the ability to carry out daily activities. It is common in older people and, according to the World Health Organization, 55.2 million people worldwide have dementia [2]. The global social cost of this condition is estimated to be approximately $1.3 trillion (2).

Hearing aids are the primary tool used in the management of hearing loss. The World Health Organization recommends the use of hearing aids when needed for mild hearing loss, with increasing levels of recommendation for moderate, severe and profound hearing loss (3). The rate of use of this tool, particularly in the hearing rehabilitation of the elderly, varies from one society to another. While in the USA the rate is 22% over the age of 80 (4), in Germany it is about 25% (5), in Denmark about 50% and in Japan about 15% (6).

Several studies have reported that hearing loss and depression are risk factors for dementia or cognitive impairment (7,8). Hearing loss leads to poor quality of life due to loneliness, social isolation, anxiety and susceptibility to depression (9). There are also several studies on the contribution of hearing aids to maintaining or slowing

Cite this article: Gülmez Mİ, Aydın C. Association of cognitive status, anxiety and depression with hearing loss in the elderly. Interdiscip Med J. 2024;15(52):86-91. https://doi.org/10.17944/interdiscip.1496779

Corresponding Author: Mehmet İhsan Gülmez, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Medical Biology, Hatay, Türkiye
Email: ihsangulmez@yahoo.com
ORCID iD: 0000-0003-0462-6353

Received: Jun 6, 2024
Accepted: Jul 30, 2024

down cognitive functions (8-10). Although hearing loss has a negative effect on cognitive functions, poor rehabilitation of hearing loss may lead to depression and cognitive impairment in elderly patients. In this study, we aimed to compare participants with and without hearing loss in terms of cognitive status, depression and anxiety, and to assess the effect of hearing aid use on this process. We hypothesised that hearing loss would lead to depression, anxiety and worsening of cognitive status.

METHOD

Between June 2023 and June 2024, 608 patients over the age of 50 who registered at the psychiatric outpatient clinic of Hatay Training and Research Hospital were included in the study. Participants were enrolled if they presented to the Psychiatry outpatient clinic during the selected time interval, were over 50 years of age and agreed to participate in the study. Participants' demographic information, educational status, social information, hearing aid use, minimental score, Beck anxiety score, and geriatric depression score were recorded. Audiometric findings were recorded by an audiometry technician using a diagnostic audiometer. In the hearing assessment, findings above the range of 0-25 dB were considered as hearing loss with reference to World Health Organization data. This study was approved by Hatay Mustafa Kemal University Ethics Committee under number 11.06.2024/01. All study participants gave informed consent.

Statistical analysis was performed using SPSS version 22.0. The data are expressed as the mean ± standard deviation (SD). Pearson's correlation coefficient was used to test the strength of the relationship between variables. Student's t-test was used to determine statistical significance between groups. For proportional correlations, the chi-squared test was used. P-values below 0.05 were considered significant.

RESULTS

The demographic information of the participants is shown in Table 1. When analyzing the educational status of the participants, 25.3% were illiterate, 74.7% were literate and had completed at least primary school. While 16.3% of the participants lived alone, 83.7% lived with family or someone else. Participants with hearing loss represented 25% of the total.

In Table 2, the participants with hearing loss are assessed within themselves. 21.9% of the participants used hearing aids. The participants with hearing loss were divided into two groups, hearing aid users and non-users. When these two groups were compared in terms of socio-demographic data, minimental test score, Beck anxiety score and geriatric depression score, no statistically significant value was found.

Table 1. Demographic characteristics of patients

Patient characteristics	Median [Range or number (%)]
Age	68 (54-88)
Gender	
Male	216 (35%)
Female	392 (65%)
Education level	
Illiterate	154 (25.3%)
Literate and primary school graduate	335 (55.1%)
Secondary school and above	119 (19.6%)
Marital status	
Married	427 (70.2%)
Widowed or Divorced or single	181 (29.8%)
Cohabitant	
Alone	99 (16.3%)
Spouse and or child or carer	509 (83.7%)
Those with hearing loss	151 (25%)
Hearing aid use	
One sided	29 (5%)
Doble sided	4 (1%)

In Table 3, individuals who used hearing aids were assessed within themselves. While 69.7% of the

participants used hearing aids regularly, the other participants did not use hearing aids regularly. 88% of the participants used unilateral hearing aids, 12% used bilateral hearing aids and 85% of the participants found hearing aids useful.

In Table 4, participants with and without hearing loss are compared in terms of demographic characteristics and test results. A significant relationship was observed between the groups in terms of age and gender. Minimal test score, Beck Anxiety Score and Geriatric Depression Score showed statistically significant results between the groups.

In Table 5, all participants were evaluated in terms of Minimental test score, Beck anxiety score and Geriatric depression score. All parameters were found to be significantly related to the Beck Depression Score. Educational status, presence of hearing loss and hearing aid use were found

Table 2. Assessing patients with hearing loss according to device usage status

Patients with hearing loss	Hearing aid users	No hearing aids	p-value
Number of patients (%)	33 (21,9%)	118 (78,1%)	
Age	73 (60-81)	71 (56-88)	0.497
Gender Male Female	 14 (42%) 19 (58%)	 51 (43%) 67 (57%)	0.898
Marital status Married Widowed or Divorced or single	 17 (51.5%) 16 (48.5%)	 80 (67.8%) 38 (32.2%)	0.102
Cohabitant Alone Spouse and or child or carer	 9 (27.3%) 24 (72.7%)	 19 (16.1%) 99 (83.9%)	0.203
Education level Illiterate Literate and primary school graduate Secondary school and above	 8 (24.2%) 20 (60.6%) 5 (15.2%)	 39 (33.1%) 63 (53.4%) 16 (13.6%)	0.62
Co-morbidity Yes No	 29 (87.9%) 4 (12.1%)	 97 (82.2%) 21 (17.8%)	0.59
Minimental Test Score (median; range)	25.5 (12-30)	25 (15-30)	0.444
Beck Anxiety Score	5 (0-19)	6 (0-18)	0.200
Geriatric Depression Score	4 (0-14)	4 (1-15)	0.680

to be significantly associated with Minimental test score. Educational status, marital status, cohabitation and presence of hearing loss were found to be significantly associated with the Geriatric Depression Score.

DISCUSSION

Hearing loss can occur at any age. It causes a reduction in social communication, an inability to understand what is happening in the environment, an inability to hear the sounds in the immediate environment, a reduction in functional capacity and ultimately a serious reduction in quality of life. It can adversely affect mental health and cognitive abilities, leading to reduced attention and concentration. When this situation is seen in older people in particular, when cognitive function begins to decline, and if adequate measures are not taken, the decline in quality of life and functional capacity can be even more shocking. There are many studies in the literature on the psychosocial impact of hearing loss. Kim S.A. et al. found that audiometric hearing loss leads to increased and worsened neuropsychiatric symptoms and worsened depressive symptoms (11). However, all of these signs and symptoms are observed to be less frequent and less severe in hearing aid users [11]. In a study by Livingstone et al, hearing loss was reported to be the most important modifiable risk factor for dementia, with a 9% risk reduction if corrected [8]. In this study, a statistically significant difference was observed when comparing the minimental test scores of participants with and without hearing loss (Table 4). The minimental test score was significantly lower in participants with hearing loss, which is consistent with the literature.

Hearing loss has long been linked to depression. Studies have shown that hearing loss can cause or aggravate depression. Han et al concluded in their study that hearing loss is associated with significantly higher depression and that this condition is more severe in patients with visual loss in addition to hearing loss (12). Brewster et al concluded that age-related hearing loss in elderly patients was associated with increased depressive symptoms after 5 years of follow-up (13). In this study, geriatric depression scores were higher in participants with hearing loss than in participants without hearing loss (Table 4). When the two groups were compared in terms of geriatric depression scores, statistically significant results were obtained (p=0.003).

There are several studies in the literature on the relationship between hearing loss and anxiety. Contrera et al. showed in their study of 1732 elderly patients that the likelihood of anxiety was higher in those with mild hearing loss compared to those without hearing loss [14]. This likelihood increased as hearing loss worsened and it was reported that hearing aid use was not significantly associated with reduced anxiety (14). Zhang et al. investigated the relationship between degree of hearing loss and anxiety and depression in patients with tinnitus in a study of 600 patients. They found a strong positive correlation between the degree of hearing loss and anxiety and depression in these patients (15). Chung et al. found that the rate of previous anxiety disorder was significantly higher in patients with sudden sensorineural hearing loss than in controls without sudden sensorineural hearing loss (16). In this study, the Beck anxiety scores were significantly higher in the group of participants with hearing loss than in the group without hearing loss (Table 4). In line with the literature, we believe that there is a significant relationship between the presence of hearing loss and anxiety.

Hearing aids are an important tool in the management of hearing loss. It is considered the main clinical intervention option, especially for patients with mild to moderate hearing loss. The main purpose of using the device is to reduce the negative consequences of hearing loss and to increase the patient's participation in daily life by facilitating and

Table 3. Demographic information and device satisfaction of hearing aid users

Hearing Aid Users	Median [Range or Number (%)]
Age	73.5 (60-81)
Gender	
Male	14 (42.4%)
Female	19 (57.6%)
Does he or she use his hearing aid every day?	
Yes	23 (69.7%)
No, it sizzles	6 (18.2%)
No, I'm losing	3 (9.1%)
No, I don't like the way it looks.	1 (3%)
Single-sided use	29 (88%)
Double-sided use	4 (12%)
Does he or she find hearing aids useful?	
Yes	28 (85%)
No	5 (15%)

improving access to speech sounds (17). Given that hearing loss is one of the modifiable risk factors for dementia, the importance of hearing aid use is better understood. Cantuaria et al. reported that hearing loss is associated with an increased risk of dementia, especially in those who do not use hearing aids, suggesting that hearing aids delay or prevent the onset or progression of dementia (18). In this study, 25% of participants had hearing loss. Of these, 21.9% used hearing aids. There are no clear data in the literature on the rate of device use in Turkey. Considering the different rates of hearing aid use in countries around the world, the rate in this study may give an idea of the rate of use in Turkey. There are several reasons for low device use among patients with hearing loss. In this study, 18.2% of the participants who used the device reported that the device made noise, 9.1% reported that they lost the device and 3% reported that they did not like its appearance. In their study. Kahveci et al reported that 56% of patients were dissatisfied with the device because of noise (19). It is important to improve the dissatisfaction-causing features of hearing aids, which are the main clinical intervention tool for patients with hearing loss, especially with regard to the health of elderly patients.

Limitations of the study

This study has several strengths and limitations. There is no study in the literature that examines the association between hearing loss and dementia, anxiety and depression and evaluates the effect of device use in a single study. The limitation of the study population can be considered a limitation. Statistically stronger data could have been obtained with a larger population. The assessment tools, especially the Beck Anxiety Scale and the Geriatric Depression Scale, are self-administered scales. Although the study team helped the participants with this, the doctor-assessed scales for older participants could have been more efficient and comprehensive.

Table 4. Comparison of patients with and without hearing loss

	Hearing loss	No hearing loss	p-value
Number of patients (%)	151	457	
Age	71 (56-88)	67 (54-86)	<0.001*
Gender			
Male	65 (43%)	151 (33%)	0.031*
Female	86 (57%)	306 (67%)	
Minimental Test Score (median; range)	25 (12-30)	26 (0-30)	0.001*
Beck Anxiety Score	5 (0-19)	4 (0-19)	0.010*
Geriatric Depression Score	4 (0-15)	3 (0-15)	0.003*

CONCLUSION

Hearing loss, especially in the elderly, reduces quality of life and contributes negatively to the development of various pathologies. In this study, a statistically significant relationship was found between hearing loss and cognitive status, depression and anxiety, and it was suggested that the use of hearing aids may be beneficial in terms of preventing the development or slowing the progression of these pathologies. It is believed that further studies with a larger population will be useful in clarifying 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.

Ethical Declaration

Ethical permission was obtained from the Hatay Mustafa Kemal University Non-Interventional Clinical Researches Ethics Committee for this study with date 11/06/2024 and number 11/06/2024/01, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: MİG, Design: MİG, CA, Supervising: MİG, Financing and equipment: MİG, CA, Data collection and entry: MİG, CA, Analysis and interpretation: MİG, Literature search: MİG, Writing: MİG, Critical review: MİG, CA.

Table 5. Scale rating of all study patients

	Minimental Test Score (median; range)	Beck Anxiety Skoru	Geriatric Depression Score
Education level			
Illiterate	24 (12-30)	5 (0-19)	6 (0-14)
Literate and primary school graduate	26 (0-30)	4 (0-19)	3 (0-14)
Secondary school and above	28 (1-30)	3 (0-19)	2 (0-15)
P value	**0.001**	**0.001**	**0.001**
Marital status			
Married	26 (0-30)	4 (0-19)	3 (0-13)
Widowed or Divorced or single	25 (12-30)	5 (0-19)	6 (0-15)
P value	0.11	**0.041**	**0.001**
Cohabitant			
Alone	25 (12-30)	5 (0-19)	7 (0-14)
Spouse and or child or carer	26 (0-30)	4 (0-19)	3 (0-15)
P value	0.108	**0.02**	**0.001**
Hearing aid use			
Yes	25 (15-30)	6 (0-18)	4 (1-13)
No	26 (0-30)	4 (0-19)	4 (0-15)
P value	**0.035**	**0.032**	0.125
Hearing loss			
Yes	25 (12-30)	5 (0-19)	4 (0-15)
No	26 (0-30)	4 (0-19)	3 (0-15)
P value	**0.001**	**0.010**	**0.003**

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CASE REPORT
DOI: 10.17944/interdiscip.1371839
Interdiscip Med J 2024;15(52):92-95

An unreported accessory muscle on the neck region

Sezgi Gürçay[1], Merve Önder[2], Gökçe Akyol[3], Nurettin Oğuz[4]

[1] Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Anatomy, Hatay, Türkiye
[2] Akdeniz University Faculty of Medicine, Department of Anatomy, Antalya, Türkiye
[3] İstanbul Medeniyet University, Prof. Dr. Süleyman Yalçın City Hospital, Department of Pediatric Surgery, İstanbul, Türkiye
[4] Girne University Faculty of Medicine, Department of Anatomy, Girne, Turkish Republic of Northern Cyprus

Abstract

An unreported accessory muscle on the neck region

Abstract

Anatomical variations or accessory muscles on the neck region are important for clinicians and surgeons. This case report aims to contribute to the literature by demonstrating the presence of a previously unrecognized muscle on the lateral neck region. During routine gross anatomy dissection of a 59-year-old male cadaver; an unreported muscle was observed next to the scalene muscles on the left lateral neck region. The distance between the center of the scalenus medius and the insertion of the muscle was 6.17 cm, and the distance between the scapular notch and the insertion of the muscle was 1.56 cm. The distance between the aponeurosis that connects the superior and the inferior bellies of the omohyoideus muscle and the first head of the muscle was 6.24 cm. This anatomical formation, which is not included in the literature, has anatomical and clinical importance in controversial clinical cases in neck pathologies.
Keywords: Accessory Muscle, Clinical Anatomy, Lateral Neck Region, Neck Surgery, Variation

INTRODUCTION

The neck is an anatomically complex region consisting of nested compartments containing structures extending from head to thorax or from thorax to head. The neck and thorax are separated by the line passing through the lower edge of the mandible, the mastoid process, and external occipital protuberant, and the line passing through the upper edge of the sternum and clavicle, the acromion and the process of the 7th vertebra separates the neck and head (1). In this region, there are many major veins and nerves, vital organs of the respiratory and digestive systems, and muscles that enable the head to move (1).

Many variations of omohyoid, digastric, sternocleidomastoid, sternothyroid, and scalene muscles have been described in the literature (2-8). In this article, a unilateral accessory muscle in the neck region, which has not been previously described in the literature, is described and its clinical and surgical significance is discussed.

CASE

During a routine gross anatomic dissection at the laboratory of the Anatomy Department of Akdeniz University, Faculty of Medicine, on the neck region of a 59-year-old male cadaver fixated in a 10% buffered formalin solution, a case of accessory muscle was observed that was unilateral and lateral to the scalenus medius muscle. This study was approved by Akdeniz University Clinical Research Ethics Committee on June 07, 2023, with decision No. KAEK-455.

After carefully removing the skin, subcutaneous tissue, superficial fascia and platysma, the muscles on the left lateral neck region were exposed. The presence of a new accessory muscle between the scalene muscles that did not fit the anatomical description was observed. The origin, insertion and shape of the muscle were investigated and its distance to other muscles was measured.

The muscle was observed between the scalenus medius and the scalenus posterior muscles and underneath the omohyoideus muscle. The muscle had two heads; the first

Cite this article: Gürçay S, Önder M, Akyol G, Oğuz N. An unreported accessory muscle on the neck region. Interdiscip Med J. 2024;15(52):92-95. https://doi.org/10.17944/interdiscip.1371839

Corresponding Author: Sezgi Gürçay, Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Anatomy, Hatay, Türkiye
Email: sezgigurcay@gmail.com
ORCID iD: 0000-0002-9061-676X

Received: Oct 5, 2023
Accepted: Feb 13, 2024

head started from the transversal process of the C4-C5 vertebrae to the posterolateral of the scalenus medius muscle. It had a long thin tendon. The second head was fan shaped and started from the insertion point of scalenus medius on the costa prima, costa secunda, and the external intercostal muscle fibers lying between these two costas. The ventral part of the first head and the second head united to form a large and common muscle mass. The common muscle mass was attached to the superior margin of the scapula, medial to scapular notch, and lateral to levator scapulae muscle. The insertion part of the muscle was located between the scapular notch and the levator scapulae muscle (Figure 1a. 1b).

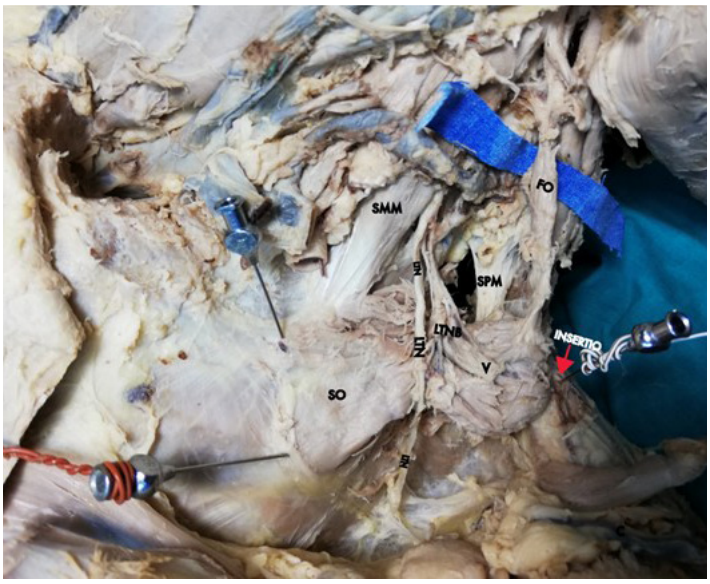

Figure 1a. Anterior view of the accessory muscle on the left neck region. FO: First origo; SO: Second origo; V: Venter; C: Clavicula; SMM: Scalenus medius muscle; SPM: Scalenus posterior muscle; LTN: Long thoracic nerve; LTNB: Branches of long thoracic nerve.

The distances between the muscle to the other neck muscles were measured with the help of Microscribe-G2x software. The distance from the belly of scalenus medius muscle to the insertions of the accessory muscle was 6.17 cm, and the distance from the scapular notch to the insertion of the muscle was 1.56 cm. The distance from the intermediate tendon of the omohyoid muscle to the first head of the accessory muscle was 6.24 cm. The accessory muscle had blood supplied by the branches of the transverse cervical artery from the left thyrocervical trunk and it was innervated by branches from the long thoracic nerve.

DISCUSSION

Anomalies of normal variants of the muscles, vessels and nerves of the neck were reported by many authors (2-16). The presence of variations and accessory structures may affect diagnostic and therapeutic procedures, making neck dissection difficult, and increasing its clinical and surgical importance.

Any variation may cause problems in reaching the desired anatomical region to be treated in some procedures. Therefore physicians, surgeons, and anesthetists performing interventional procedures in the neck region should be aware of the possible variations of the origin and insertion of both these muscles and the accessory muscles that have not been classified and reported in the literature. In addition, variational muscles' may exert pressure on underlying structures during, and this may occur in different clinical situations.

Mansoor et al. (4), in the examination of a patient with neck and shoulder pain, torticollis, limitation of neck movements, and pain in long-term posture determined that the right sternocleidomastoid muscle had an accessory clavicular head. The origin and insertion of the identified accessory muscle may restrict the right rotation and lateral flexion of the head. In patients who apply to the clinic with the complaint of limitation of rotation and lateral flexion of the head, the patient should be approached by considering the presence of such accessory muscles. Diagnosis and treatment processes should be planned considering the existence of such variations. We think that the use of musculoskeletal ultrasound examination in the differential diagnosis will be helpful when evaluating patients with these complaints.

Natsis et al. (6) stated that unilateral or bilateral asymmetric muscle variations in the submental region is clinically significant because they can sometimes be confused with enlarged lymph nodes, benign cervical masses, or neoplasia.

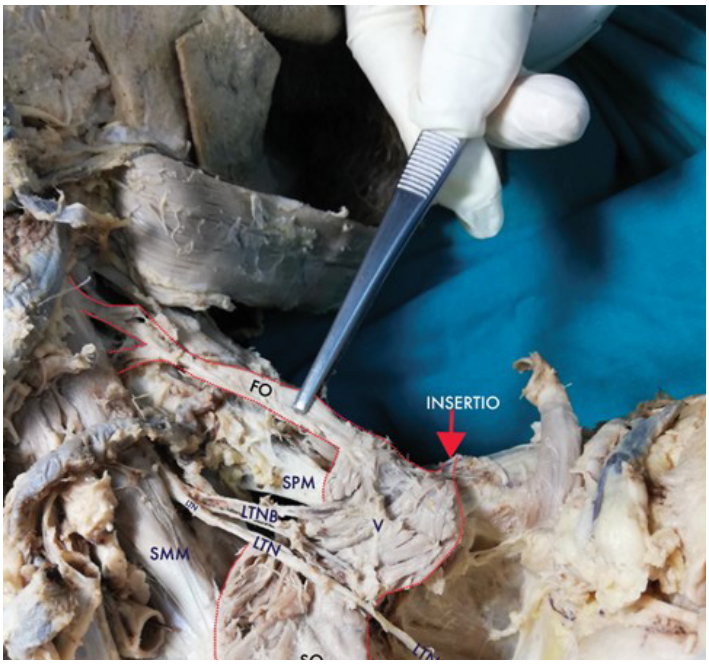

Figure 1b. Anterior view of the accessory muscle on the left neck region. FO: First origo; SO: Second origo; V: Venter; C: Clavicula; SMM: Scalenus medius muscle; SPM: Scalenus posterior muscle; LTN: Long thoracic nerve; LTNB: Branches of long thoracic nerve. (In fig. 1b, the borders of the accessory muscle are surrounded by punctuation for easier understanding).

Muscle variations and accessory muscles in the neck area can also be confused with masses (6, 14-16). Variations of structures in the neck area had also radiological importance, especially when computed tomography or magnetic resonance imaging is used in the detection and staging of tumors. It is essential to be able to distinguish between tumors, metastatic lymph nodes, and muscle variations. Because not all asymmetrical images show tumors, clinicians should be careful to avoid misinterpretation. Variations can easily be misinterpreted as a false mass or a normal or metastatic lymph node (15, 16). Therefore, advanced imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging should be used in the differential diagnosis of masses.

CONCLUSION

This case, which is not included in the literature, has anatomical and clinical importance in neck pathologies, controversial clinical cases and when performing procedures in the lateral neck. Therefore, the need to understand muscle variation is more important than ever to avoid iatrogenic injuries when performing surgery or examining the neck.

Such variations may be of concern to surgeons and anesthesiologists performing interventional procedures on the neck region due to the confusion of local anatomical landmarks. Information about the variations, anomalies of the muscles on the neck region and the accessory muscles newly defined in the literature is extremely important for doctors who are interested in the diagnosis and treatment of the problems on the neck region.

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.

Previously Report

The authors declared that some part of this study was presented as a poster at "20th National Anatomy Congress" held in İstanbul, entitled "Kadavra Boyun Bölgesinde Aksesuar Kas".

Ethical Declaration

This study was approved by the Akdeniz University Clinical Research Ethics Committee on June 07, 2023, with decision No. KAEK-455.

Authorship Contributions

Concept: SG, MÖ, GA, NO, Design: SG, MÖ, GA, Supervising: SG, NO, Financing and equipment: -, Data collection and entry: SG, MÖ, Analysis and interpretation: SG, MÖ, Literature search: SG, MÖ, Writing: SG, MÖ, Critical review: SG

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CASE REPORT
DOI: 10.17944/interdiscip.1409955
Interdiscip Med J 2024;15(52):96-98

Unusual finding on bone scintigraphy: Cerebral 99m-tc mdp involvement

Edanur Ekinci, Ebuzer Kalender, Yusuf Burak Çayırlı

Gaziantep University Faculty of Medicine, Department of Nuclear Medicine, Gaziantep, Turkey

Abstract

Unusual finding on bone scintigraphy: Cerebral 99m-tc mdp involvement

^{99m}Tc-MDP (99mTc-methylene diphosphonate) uptake in the brain parenchyma was observed in the scintigraphic imaging of a 56 years old male patient with renal cell carcinoma (RCC), who was referred to our clinic for metastasis screening due to widespread bone pain. Uptake of ^{99m}Tc-MDP in the brain parenchyma in bone scintigraphy is a rare finding. This case is presented to reveal the causes of cerebral 99mTc-MDP involvement.

Keywords: bone scintigraphy, ^{99m}Tc-MDP, serebrovascular event

INTRODUCTION

Bone scintigraphy is a frequently used examination in nuclear medicine applications. It is widely used to screen suspected bone metastases of various cancers due to its easy accessibility and low cost (1-4). In addition, osteoarticular infections (osteomyelitis, prosthetic infections, etc.), metabolic bone diseases and traumatic pathologies (stress fracture, pseudoarthrosis, etc.) are among the main clinical indications (5).

Technetium-99m (^{99m}Tc)-labeled diphosphonates, particularly ^{99m}Tc-methylene diphosphonate (MDP), are the most widely used radiopharmaceuticals in bone scintigraphy (1-4). Although the mechanism of uptake is not yet fully understood, diphosphonates bind to hydroxyapatite crystals on mineralized bone surfaces (1,6,7). A lesser part is bind to the organic matrix of bone, immature collagen tissue. High osteoblastic activity, characterized by local bone blood stream, increased permeability, increased bone surface area, and new bone formation, plays an active role in the uptake of phosphonates in bone tissue (8).

Extraosseous ^{99m}Tc-MDP uptake can also be observed in bone scintigraphy in such cases: benign or malignant soft tissue calcifications, hematomas, soft tissue infections and inflammations, etc . Although cerebrovascular events (CVE) are common in the population, brain parenchyma involvement is an unusual finding in bone scintigraphy (9). In our patient with RCC who underwent whole body bone scintigraphy for metastasis screening, activity involvement was observed in the brain parenchyma, and the reasons for this were tried to be explained with this case report.

CASE

A 56-year-old male patient with RCC was referred to our clinic for whole body bone scintigraphy due to widespread bone pain.

The patient was intravenously injected with 20 mCi (740 MBq) of ^{99m}Tc-MDP. After 3 hours, the whole body was scanned with a double-headed gamma camera with a low-energy and high-resolution collimator attached and integrated with a computed tomography (CT) device.

Slightly irregular increased ^{99m}Tc-MDP uptake in both sacroiliac regions and vertebral column in the scintigraphy examination was initially evaluated in favor of osteodegenerative changes. Except this, heterogeneous ^{99m}Tc-MDP uptake were observed in the mid-level of the left half of the neurocranium (Figure 1).

Cite this article: Ekinci E, Kalender E, Çayırlı YB. Unusual finding on bone scintigraphy: Cerebral 99m-tc mdp involvement Interdiscip Med J. 2024;15(52):96-98. https://doi.org/10.17944/interdiscip.1409955

Corresponding Author: Edanur Ekinci, Gaziantep University Faculty of Medicine, Department of Nuclear Medicine, Gaziantep, Turkey
Email: eda.nur.eknci@hotmail.com
ORCID iD: 0000-0003-3850-5816

Received: Dec 25, 2023
Accepted: May 4, 2024

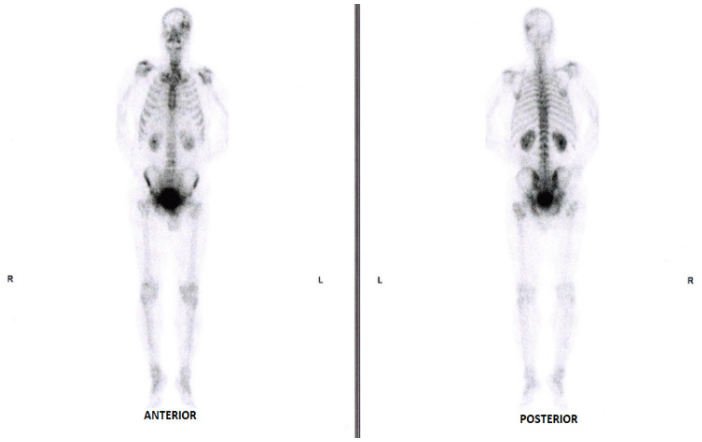

Figure 1. Patient's whole body bone scintigraphy, anterior and posterior images. Suspected ^{99m}Tc-MDP uptake was observed in the mid-level of the left half of the neurocranium. In addition, slightly increased ^{99m}Tc-MDP uptake was observed in both sacroiliac joints and vertebral column suggesting osteodegenerative changes. Activity distributions in other bones of the skeletal system were at normal range (Gaziantep University Faculty of Medicine, Department of Nuclear Medicine)

Because of this involvement, the patient underwent SPECT/CT hybrid imaging of the cranial region. In SPECT/CT imaging, it was understood that 99mTc-MDP uptake was not in the bone structure but in the left frontotemporal region within the brain parenchyma. In addition, heterogeneous density changes were observed in this area in CT sections (Figure 2).

When the patient's history was examined, it was learned that he had CVE about 2 weeks before the date of bone scintigraphy and angiography was performed for the left middle cerebral artery.

DISCUSSION

Bone scintigraphy is an examination with high sensitivity and low specificity. However, the morphological information provided by single-photon emission computed tomography (SPECT)/computed tomography (CT) hybrid systems greatly increased the specificity of the method.

Extraosseous ^{99m}Tc-MDP involvement in bone scintigraphy can be seen in benign or malignant soft tissue calcification areas. Such formations of the calcium deposits in soft tissue can be a result of conditions that cause dystrophic calcification as in ectopic osteoblastic activity, metastatic calcification, osteoid formation in some tumors, excess ions such as iron and magnesium to which calcium binds, hypoxemia or amyloid. Metastatic calcification occurs when diphosphonates precipitate in the tissues in case of hypercalcemia. It is often seen with increased secretion of parathormone (PTH), bone destruction or vitamin D

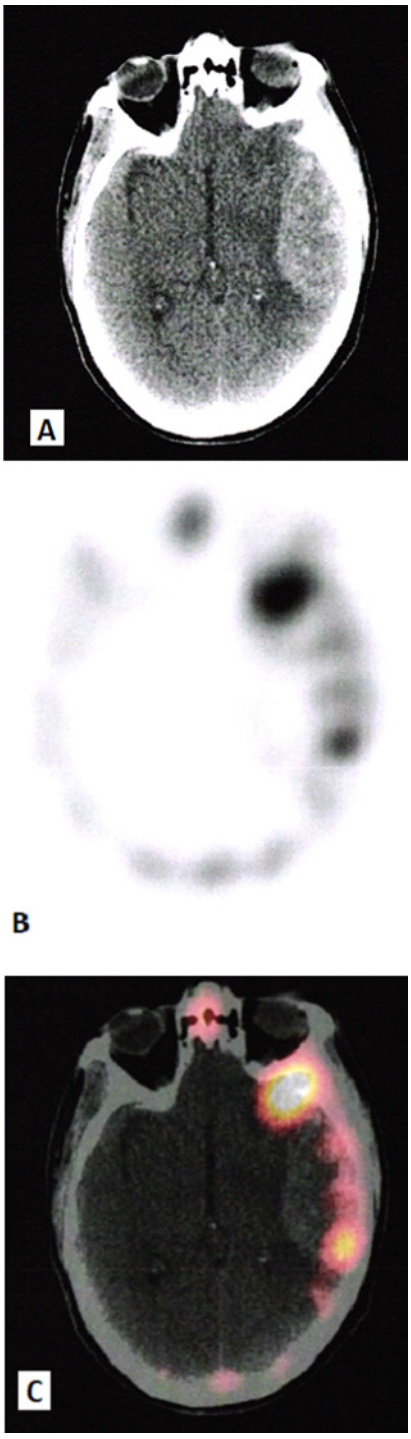

Figure 2. Cranial images of the patient: Transaxial CT (A), Transaxial SPECT (B), Transaxial SPECT/CT (C) fusion images show increased 99mTc-MDP uptake in the heterogeneous area of the brain parenchyma in the area matching the left frontotemporal region (Gaziantep University Faculty of Medicine, Department of Nuclear Medicine)

metabolism disorders. Diphosphonate uptake is observed especially in organs with high pH values such as kidneys and lungs. Dystrophic calcification, on the other hand, refers to the accumulation of calcium in the tissue due to trauma, ischemia, or cellular necrosis, while serum calcium and phosphate levels are normal. Diphosphonate uptake due to

infarction in the heart, brain or muscle tissue is an example of this (8,10).

^{99m}Tc-MDP also accumulates in ischemic tissues due to intracellular calcium accumulation resulting from cell membrane damage and protein denaturation (11). Although CVE is a common disease, brain parenchyma involvement in bone scintigraphy is an unusual finding in these cases. Moreover, in addition to microcalcification or bleeding, disruption of the blood-brain barrier is one of the main factors affecting this involvement. It has been stated that this abnormal appearance in the brain parenchyma may return to normal approximately 4 months after the infarction (9).

In this case, ^{99m}Tc-MDP uptake in the brain parenchyma as a rarely seen extraosseous involvement in whole body bone scintigraphy was presented. In the case with a history of CVE, it was thought that ^{99m}Tc MDP uptake in the brain parenchyma was caused by intracellular calcium accumulation due to cell membrane damage and, more likely, the disruption of the blood-brain barrier due to CVE.

In addition, this case showed us the importance of detailed and accurate history of the patient in bone scintigraphy, and the high efficiency of SPECT/CT imaging for diagnosis.

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.

Previously Report

The authors declared that some part of this study was presented as a poster at "20th National Anatomy Congress" held in İstanbul, entitled "Kadavra Boyun Bölgesinde Aksesuar Kas".

Ethical Declaration

The authors declare that informed consent was obtained from the participant for the conduct of this study and that the rules of the Declaration of Helsinki were followed.

Authorship Contributions

Concept: SG, MÖ, GA, NO, Design: SG, MÖ, GA, Supervising: SG, NO, Financing and equipment: -, Data collection and entry: SG, MÖ, Analysis and interpretation: SG, MÖ, Literature search: SG, MÖ, Writing: SG, MÖ, Critical review: SG

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